INFECTIOUS DISEASES
AND TROPICAL MEDICINE








Dr. Ibrahim Ashour Hamed

Imbaba fever hospital

BACTERIAL DISEASES

Group	Genus	Examples
Gram positive cocci	Staphylococcus	S.aureus, S. epidermidis, S. saprophyticus
	Streptococcus	S. pneumoniae, S. pyogenes, E. faecalis
	Micrococcus	----------
	Peptococcus and peptostreptococcus	----------
Gram positive bacilli	Bacillus	B. anthracis, B. cereus
	Corynebacterium	C. diphtheriae
	Listeria	L. monocytogenes
	Lactobacillus	----------
	Clostridium	C. difficile, C. botulinum, C. perfringens, C. tetani
	Propionibacterium	P. acnes
	Actinomyces	A.israeli
	Nocardia	N. asteroides
Gram negative cocci	Neisseria	N. gonorrhoeae, N. meningitidis
	Veillonella	----------
Gram negative bacilli	Enterobacter	E. chloaceae
	Escherichia	E. coli
	Klebsiella	K. pneumoniae
	Proteus	P. mirabilis
	Salmonella	S. typhimurium
	Serratia	S. marcescens
	Shigella	S. sonnei
	Yersinia	Y. enterocolitica
	Pseudomonas	P. aeruginosa
	Vibrio	V. cholerae, V. parahaemolyticus
	Campylobacter	C. jejuni
	Helicobacter	H. pylori
	Bordetella	B. pertussis
	Brucella	B. abortus, B. melitensis
	Haemophilus	H. influenzae, H. parainfluenzae
	Pasteurella	P. multocida
	Legionella	L. pneumophila
	Bacteroides	B. fragilis
	Fusobacterium	----------
Spiral bacteria	Borrelia	B.vincenti and leptotrichia buccalis , B. recurrentis
	Treponema	T. pallidum, T. pertenue
	Leptospira	L. canicola, L. icterohaemorrhagiae
Acid fast bacilli	Tubercle bacilli	M. tuberculosis, M. bovis
	Leprosy bacillus	M.leprae
	Atypical mycobacteria	M. avium, M. kansasii
Cell wall deficient bacteria	Mycoplasma pneumoniae	----------
	Ureaplasma urealyticum	

MENINGITIS

Cryptococcal meningitis

Causative organism

1- **Cryptococcus neoformans** (yeast like fungus)

2- There are **3 varieties of the organism**

- Var grubii and var neoformans → occur worldwide and are found in the environment related to avian droppings
- Var gatti → occur in the tropics and found in association to eucalyptus trees

Risk factors

1- It occurs in both immunocompetent and immunocompromised hosts (i.e. HIV-infected patients, prolonged steroid, etc.)

2- It occurs in HIV-infected persons predominantly when **CD-4 cell count is < 100×10^6 /L**

3- Diabetes mellitus, end stage renal disease and liver cirrhosis are the main associated conditions in the patients without HIV

Mode of transmission

1- Infection is acquired by **inhalation**

2- predominantly causes

- Pneumonia or
- Cryptococcal meningitis

Clinical features

1- **Pneumonia** (cough, dyspnea):

- Less common
- Often asymptomatic or mild and may resolve spontaneously
- Rapidly progressive pulmonary illness in a small no. of immunocomp. Pt

2- **Subacute or chronic meningitis**

- Fever, headache, altered mental status of several weeks duration
- Neck rigidity is relatively uncommon
- Cranial nerve palsies, visual disturbance associated with papilloedema
- The diseases may be indistinguishable clinically from TB meningitis

3- **Disseminated disease** (in advanced immunosuppression)

4- **Skin lesions** may occur and may contain the organism

Diagnosis

1- **High suspicion** should be maintained in HIV-infected persons with unexplained fever or headache

2- **CSF analysis** shows:

- Increased opening pressure
- ↑ proteins and glucose ↓
- ↑ WBCs (moderate pleocytosis) with a predominant Lymphocytosis
- Cell count and protein can be normal
    - In early infection or
    - In advanced immunosuppression

3- **The organism** can be detected by:

- CSF staining by Gram-stain or Indian-ink stain.
- Cultures of CSF, blood or occasionally skin lesion

4- Cryptococcal polysaccharide **antigen** detection in CSF or blood by latex agglutination with high sensitivity

Treatment

1- **Optimum treatment**

- Combination of amphotericin B (1 mg/kg/day) & flucytosine (100 mg/kg/day) for 2 weeks
- Followed by fluconazole (400 mg/day) for 8 weeks

2- Treatment in resource- poor settings

- Amphotericin B cause renal toxicity and Flucytosine cause bone marrow depression, so both drugs need close monitoring
- Fluconazole 400 mg or more daily may be used, but has 2 disadvantages
  - Takes much longer time to sterilize the CSF
  - Associated with higher relapse rate

3- Reduction of the intracranial pressure

- Many clinicians advocate repeated lumbar puncture

4- Prevention of relapse in HIV patients:

- Fluconazole (200 mg/day) continued for life or until CD-4 cell count is $> 200\times10^{6}$ /L for several months after antiretroviral treatment

5- Time of initiation of **antiretroviral therapy** in HIV patients

- If initiated shortly after treatment → may be associated with cryptococcal immune reconstitution inflammatory syndrome in 8-50% of cases (IRIS) → sudden onset deterioration with worsening meningitis symptoms and progression or development of new neurological symptoms.
- Better clinical outcomes occur if ART is initiated after 6 months of diagnosis of cryptococcal meningitis

TB meningitis

Causative organism → Mycobacterium tuberculosis

Source of infection

1- Usually it is **secondary** to a primary tuberculous focus present in mediastinal or mesenteric lymph nodes, in the lung or in the genitor-urinary system

2- Sometimes the primary focus can't be detected

Risk factors

1- Age (children > adults)

2- HIV- coinfection

3- Disease prevalence in the community

4- Malnutrition and Alcoholism

5- Recent measles in children

6- Malignances and immunosuppressive agents

Clinical features [vary from one case to onother]

1- Prodromal stage:

- Characterized by slow onset and vague indefinite symptoms
- Anorexia, headache, vomiting and periods of drowsiness are common

2- Transitional stage:

- Characterized by evidence of meningeal irritation in the form of bulging fontanelles, nuchal rigidity and stiffness of the back
- Deep reflexes are exaggerated and ocular paralysis is common
- Photophobia or convulsions may occur

3- Terminal stage:

- Characterized by the occurrence of coma with cessation of voluntary movements
- Death occurs from medullary failure

Diagnosis

1- Clinical

- Fever and headache (for more than 14 days)
- Vomiting
- Irritability, altered sensorium or focal neurological deficit
- Weight loss and cachectic patient
- May be history of TB (10%), positive tuberculous contact history is important

2- CSF

- Clear or hazy under high tension
- If CSF is left for sometime → cob web appearance may be detected
- Pleocytosis (> 20 cells, more than 60% lymphocytes)
- Increased proteins (> 100 mg/dl)
- Low sugar (< 60% of corresponding blood sugar)
- India ink studies and microscopy for malignant cells should be negative

3- A highly positive **tuberculin skin** test is suggestive

4- Detection of tubercle bacilli in CSF by **PCR** is highly specific and sensitive in about 85% of cases. Adenosine deaminase test for CSF is more sensitive than PCR

5- Imaging مهم

- Exudates in basal cisterns or in sylvian fissure hydrocephalus
- Infarcts (basal ganglionic)
- Gyral enhancement
- Tuberculoma formation

6- Evidence of tuberculosis elsewhere

- Chest X-ray may reveal primary complex, hilar glands or military tuberculosis (active pulmonary tuberculosis on chest X- ray ranges from 30 to 50%)
- Fundus examination may reveal choroidal tubercles which is an immediate diagnostic facility

Differential diagnosis

1- Partially treated early bacterial meningitis

2- Cryptococcal meningitis

3- Listeria monocytogenes meningitis

Complications

1- Complete **blindness** in about 5% of cases

2- **Optic pallor** in about 5% of cases

3- **Paraplegia or hemiplegia** due to occurrence of granulation tissue around the spinal cord

4- Obstructive **hydrocephalus** may occur esp. in children

Treatment

1- **Recent recommended treatment regimen** for CNS tuberculosis caused by fully susceptible M. tuberculosis: treatment for 1 year or more

Drug	Daily dose children	Daily dose adults	Duration
Isoniazid	10-20 mg/kg	300 mg	10 to 12 months
Rifampicin	10-20 mg/kg	450 mg (<50 kg) 600 mg (>50 kg)	10 to 12 months
Pyrazinamide	15-30 mg/kg	1.5 g (<50 kg) 2.0 g (>50 kg)	2 months
Ethambutol	15-20 mg/kg	15 mg/kg	2 months

2- **Adjunctive corticosteroids therapy:**

- All patients with TBM should receive corticosteroids regardless of disease severity at presentation
- Adults (>14 years) should start treatment with dexamethasone 0.4 mg/kg/24 hours with a tapering course over 6 - 8 weeks
- Children (d”14 years) should be given prednisolone 4mg/kg/24 hrs (or equivalent dose dexamethasone: 0.6 mg/kg/24 hrs) for 4 weeks, followed by a tapering course over 4 weeks

3- **<u>If drug-induced hepatitis occurs</u>**, and if serum transaminases rise above 5 times normal:

- Stopping pyrazinamide, continuing isoniazid, rifampicin, ethambutol, and performing daily liver function tests is recommended.
- If serum albumin falls, the prothrombin time rises, or the transaminases continue to rise, isoniazid and rifampicin should be withdrawn.
    - Streptomycin and ethambutol should be given, along with moxifloxacin or levofloxacin [Streptomycin: 25 mg/kg/day I.M. max. 1 g/day]
    - Rifampicin and isoniazid should be restarted once the liver function tests are normal

4- Bed rest, **<u>nutritious diet</u>** and vitamins esp. vitamin B6 are important

5- **<u>Response of therapy</u>** is indicated by:

- Drop of fever.
- Regain of alert mental status
- Rise of CSF sugar.
- Decreases of cell count & proteins

Eosinophilic meningitis

Definition

1- It's a rare entity with the key criteria that the CSF shows the presence of an increased number of **eosinophil** in a patient with clinical manifestations of meningitis.

2- The most common causes of eosinophilic meningitis worldwide are the parasitic infections caused by **nematodes**

Etiology

1- Parasitic causes

The causative organism	Mode of transmission
▪ **Angiostrongylus cantonensis** (rat lung nematode) [commonest cause]	Eating undercooked seafood (e.g. crabs, prawns & snails) containing larvae
▪ Baylisascaris procyonis (baylisascariasis) [the commonest cause in USA]	Eating food contaminated with raccoon feces
▪ Gnathostoma spinigerum (intestinal nematode of cats & dogs)	Eating undercooked fish.
▪ Coccidiodes immitis (protozoa) [the most common nonparasitic infectious cause]	Respiratory route.
▪ Schistosoma (trematode)	
▪ Cysticercosis (cestode)	
▪ Toxocariasis (nematode)	
▪ Paragonimiasis (trematode)	

Sporadic cases in Southeast Asia, South Pacific and the Caribbean

Eosinophilic meningitis occurs as a result of larval migration within the nervous system

2- Non-parasitic causes:

- Aspergillosis (fungus), transmitted by respiratory route
- Myeloproliferative diseases [hematologic malignancies or metastatic cancer]
- Ventriculoperitoneal shunts can also cause an increase in eosinophilia in the CSF
    - The commonest cause in pediatrics

- Patients with Propionibacterium acnes-induced shunt infections have higher eosinophil percentages than are found in infections associated with other organisms

- Contrast myelography

Clinical features

1- Presence of persistent headache and eosinophilia in travelers coming from developing countries or residents of Asia should raise the **index of suspicion** for eosinophilic meningitis due to parasites

2- A thorough **travel and food history** should be performed on all patients suspected with eosinophilic meningitis

3- **Severe headache** (the commonest complaint, attributed to intracranial pressure).

4- **Nausea, vomiting and neck stiffness** are frequent.

5- **Paresthesias** of the thorax and extremities are seen

6- **Altered consciousness** and generalized weakness are rare.

7- **Fever** is not a prominent symptom even in infection.

8- **Other nonspecific symptoms** include visual disturbances, photophobia, arthralgias, myalgias, GI and respiratory symptoms.

Diagnosis

1- **CSF analysis:**

- Eosinophilia either > 10 eosinophils/mm^3 or > 10% of the total CSF leukocytes in a patient with symptoms of meningitis.
- The CSF shows leukocyte counts in the range of 20-5000 cells (usually 150-2000).
- Wrights solution or Giemsa stain is commonly used to visualize the CSF eosinophilia.
- Peripheral blood eosinophilia does not correlate with CSF eosinophilia.
- CSF eosinophilia is usually 20 – 70%
- Normal or minimally low glucose and slightly elevated CSF Protein

- In eosinophilic meningitis due to parasites, eosinophila pleocytosis peaks at weeks 1-2 and then gradually resolves over several months
- Opening pressure is variable

2- CSF ELISA and Serum ELISA

- For Angiostrongylus cantonensis, have the highest accuracy

3- Anaerobic culture of CSF → in suspected cases of eosinophilic meningitis in patients with shunts

4- Ophthalmological exam

- Screen for presence of ↑ intracranial pressure
- Larvae may be seen in the eye

5- Examination of peripheral **blood smear and bone marrow aspiration**:

- Indicated if infection cannot be confirmed and if no evidence of spinal cord or CSF manipulation has occurred to exclude underlying hematological disease

6- CT and MRI to exclude other potential causes of meningitis.

Treatment

1- The disease is usually **self-limiting** if the cause is infectious or due to spinal cord manipulation, although some symptoms including headache may persist for > 4 weeks

2- Most of the patients can be adequately managed with supportive therapy with **analgesics plus rehydration**

- NSAIDs should be avoided since they are occasionally the direct cause of CSF pleocytosis and headache

3- Corticosteroid therapy provides symptomatic relief of refractory headaches

- Dose: 60 mg prednisolone/day for 2 weeks

4- In patients with increased intracranial pressure, **serial lumbar punctures** may produce major clinical improvement.

5- Antihelminthic agents are commonly prescribed for parasitic infection (e.g. albendazole or mebendazol or praziquantel) ®

- But they are contraindicated or should be used with caution as it may exacerbate neurologic symptoms because of larvae death within the CSF

6- <u>Antifungal treatment</u> for aspergillosis ®

Bacterial meningitis

Definition

1- <u>Suspected acute bacterial meningitis</u>

- Sudden onset of fever (>38.5°C rectal or 38.0 axillary)
- + one or more of the following:
  - Stiff neck
  - Altered consciousness
  - Other meningeal signs or petechial or purpural rash (in patients < 1 year of age, ever accompanied by a bulging fontanel).

2- <u>Confirmed bacterial meningitis:</u>

- A suspected case
- + Turbid CSF
- And the following results:
  - Meningococcal; gram stain showing gram-negative diplococcus, ongoing epidemic.
  - Pneumococcal; gram stain with gram positive cocci.
  - H.influenza; gram stain showing gram negative pleomorphic rods
- Or acase with laboratory confirmation (either CSF culture or CSF antigen detection)

Etiology

1- <u>Premature babies and newborn up to 3 months old:</u>

- <u>Group B streptococci</u> (subtypes III which normally inhabit the vagina and are mainly the cause during the first week of life)
- <u>Escherichia coli</u> (carrying K1 antigen) that normally inhabit the digestive tract

- Listeria monocytogenes (serotype 1V-b) may affect the newborn and occurs in epidemics

2- Infants and children:

- Neisseria meningitides
- Streptococcus pneumoniae (serotypes 6,9,14,18,23)
- Haemophilus influenzae type B (under 5 years in countries that do not offer vaccination).

3- Adults:

- Neisseria meningitides and Streptococcus pneumoniae (together cause 80% of all cases of bacterial meningitis).
- Listeria monocytogenes (increased risk in those over 50 years old).

4- Less common pathogens and predisposing factors

Predisposing factor	Common bacterial pathogens
Immunocompromised state	S. pneumoniae, N. meningitides, L. monocytogenes, aerobic gram-negative bacilli (including pseudomonas aeruginosa)
Basilar skull fracture	S.pneumoniae, H. influenzae, group A B- hemolytic streptococci
Head trauma	Staphylococcus aureus
Post-neurosurgery	Stapyhlococcus epidermidis, aerobic gram-negative bacilli (including P. aeruginosa)
Cerebrospinal fluid shunt	S. epidermidis, S. aureus, aerobic gram-negative bacilli (including P.aeruginosa, escherichia coli, klebsiella species, acinetobacter), Propionibacterium acnes.

Epidemiology of ABM in Egypt

1- Pneumococcal Meningitis

- Currently the Leading Cause of Meningitis in Egypt

2- Neisseria meningitidis

- Was for long reported as the leading cause for bacterial meningitis in Egypt
- Recently it was described as the second or third leading cause after S. pneumonia
- The decrease in the number of meningococcal meningitis may due to

- The introduction of school-based vaccination program using the bivalent A/C polysaccharide vaccine for children upon entry of primary school and a second dose of vaccine 3 years after school entry with a coverage of more than 95% in the past 5 years.
- The mandatory meningococcal vaccination for all persons before leaving to attend the Hajj in addition to the immunization programs of military recruits

3- **H. influenza:**

- The leading cause of meningitis in very young children

Clinical features

1- **Severe headache:** is the most common symptom of meningitis in adults occurring in almost 90% of cases of bacterial meningitis

2- **Nuchal rigidity:** (inability to flex the neck forward passively due to increased neck muscle tone and stiffness) occurs in 70% of adult cases of bacterial meningitis

3- **Fever:** occurs in 75-85% of patients

4- **Altered mental status:** occurs in 75% of patients and can vary from lethargy to coma

5- **The classic triad of diagnostic signs consists of:** nuchal rigidity, sudden high fever, and altered mental status however, all three features are present in only 44–46% of all cases of bacterial meningitis. If none of the three signs is present, meningitis is extremely unlikely**.** But at least two of possible tetrad of headache, fever, neck stiffness and altered mental status occur in 95%

6- **Atypical presentation** may be observed in certain groups.

- Elderly individuals, especially those with underlying co-morbidities (e.g., diabetes, renal and liver disease), may present with lethargy and an absence of meningeal symptoms.
- Patients with neutropenia may present with subtle symptoms of meningeal irritation

7- **Positive Kernig's sign or Brudzinski's sign:**

- Kernig's sign is assessed with the patient lying supine, with the hip and knee flexed to 90 degrees. In a patient with a positive Kernig's sign, pain limits passive extension of the knee.
- A positive Brudzinski's sign:
  - Neck sign → flexion of the neck causes involuntary flexion of the knee and hip.
  - Leg sign → flexion of the lower limb on one side results in similar movement on the opposite side
- Although Kernig's and Brudzinski's signs are both commonly used to screen for meningitis, the sensitivity of these tests is limited**.**

8- **Jolt accentuation maneuver:** Another test helps to determine whether meningitis is present in patients reporting fever and headache. The patient is told to rapidly rotate his or her head horizontally; if this does not make the headache worse, meningitis is unlikely

9- **Other common symptoms of meningitis:** include vomiting, and an inability to tolerate light (photophobia) or loud noises (phonophobia)

10- **Seizures:**

- Occur in 5% to 28% of adults who have meningitis
- Seizures are the presenting symptom in one-third of pediatric patients who have bacterial meningitis. In childhood meningitis, seizures occur more frequently with S pneumoniae and H influenzae B than with meningococcal meningitis

11- **Meningococcal meningitis:**

- Can be differentiated from meningitis with other causes by a rapidly spreading petechial rash which may precede other symptoms
- The rash consists of numerous small, irregular purple or red spots "petechiae" on the trunk, lower extremities, mucous membranes, conjunctiva, and (occasionally) the palms of the hands or soles of the feet.

- The rash is typically non-blanching: the redness does not disappear when pressed with a finger or a glass tumbler.
- Although this rash is not necessarily present in meningococcal meningitis, it is relatively specific for the disease; however, occasionally occur in meningitis due to other bacteria
- The rapid development of hemorrhagic eruptions in conjunction with shock almost certainly indicates meningococcemia

Complications

1- **Meningococcemia:** the patient has certain characteristics

- Deep coma in a short time.
- Rash mostly purpuric.
- Manifestations of shock.
- No signs of meningeal irritation.
- Positive blood culture in most of the cases.

© The mortality rate of meningococcal meningitis in Egypt ranges between 3-10%. Meningococcemia has the highest mortality rate

© Hemorrhage of the adrenal glands, leading to Waterhouse-Friderichsen syndrome, which is often lethal in severe meningococcal and pneumococcal infections

2- **Neurological sequlae include:**

- Convulsions either focal or generalized.
- Cranial nerve affections especially third, fourth, sixth and seventh nerves in about 8-14% of cases of bacterial meningitis.
- Marked cerebral oedema.
- Focal cerebral signs: hemiparesis, hemiplegia and dysphagia may occur in about 15% of cases of bacterial meningitis.
- Fundus complications: as visual field defects and post-papilloedemic optic atrophy.
- Subdural effusion and post basic meningitis may occur especially in infants and children.

- Hydrocephalus: due to obstruction of the normal flow of the CSF around the brain as a result of inflammation of the brain tissues
- Encephalitis, cerebral vasculitis and cerebral venous thrombosis
- After bacterial meningitis, patients are at high risk of cognitive impairment. Studies on cognitive impairment among adults after bacterial meningitis described cognitive slowness, impairment of psychomotor performance, reduction in visuo-constructive performance and higher scores on depression scales

3- **Non- neurological sequlae include:**

- Sepsis: may be triggered by the infection which is a systemic inflammatory response syndrome characterized by hypotension, tachycardia, high fever or hypothermia and rapid breathing
- Disseminated intravascular coagulation (DIC): the excessive activation of blood clotting, may cause both the obstruction of blood flow to organs and a paradoxical increase of bleeding risk. In meningococcal disease, gangrene of limbs can occur
- Shock and septic complications

Differential diagnosis

1- **General infections associated with toxaemia:** as influenza, pneumonia and enteric fevers. Headache is a prominent feature with negative signs of meningeal irritation

2- **Meningism:** may occur in the course of

- Infectious diseases: as influenza, pneumonia, otitis media and enteric fevers. There are positive signs of meningeal irritation but the CSF is under tension, clear with no significant pleocytosis
- Non-infectious causes: as in cases of posterior inferior cerebellar artery thrombosis

3- **Subarachnoid hemorrhage:** usually presents by sudden violent headache, brief or prolonged loss of consciousness, fever, diplopia, ophthalmoplegia, fundus

examination may reveal flame shaped haemorrhage in the retina, CSF is under tension and bloody and CAT scan of the brain is very helpful in the diagnosis

4- **Aseptic meningitis**

5- **Heat stroke**

6- **Brain tumors**

7- **Botulism**

Diagnosis (LP)

1- If meningitis is a consideration, a **lumbar puncture must be performed**.

2- If focal neurologic deficits and papilledema are present, **CT scan** should be performed before a lumbar puncture.

3- CSF characters of bacterial meningitis:

- Physically:
  - Increased opening pressure
  - Aspect is turbid
- Cyto - chemically:
  - Cells: > 90% polymorphonuclear leukocytes (except with Listeria).
  - Protein: is elevated 150-1000 mg/dl
  - Glucose: is decreased < 25 mg/dl (< $^{2}/_{3}$ of serum value)

4- Other CSF studies

- CSF stain:
  - Gram stain for bacteria
  - Ziehl-Neelsen or auramine stain for TB (should be performed if CSF is lymphocytic).
  - Indian-ink stain for cryptococcal (should be performed if CSF is lymphocytic).
- CSF and blood cultures allow for antibiotic sensitivity testing
- CSF PCR: for detection of bacterial DNA
- Detection of bacterial antigens in CSF by latex agglutination (LA) test
- The Limulus amebocyte lysate assay:

- It's a rapid diagnostic test for the detection of gram-negative endotoxin in CSF (diagnosis of gram-negative bacterial meningitis).
- The test has a specificity of 85–100% and a sensitivity approaching 100%.

5- Neuro-imaging:

- Almost all patients with bacterial meningitis will have neuroimaging studies performed during the course of their illness
- MRI is preferred over CT because of its superiority in demonstrating areas of cerebral edema and ischemia

CSF findings suggestive of bacterial meningitis are

1- Positive Gram's stain (organism identified on slide).
2- Glucose less than 40 mg/dl or ratio of CSF/blood glucose less than 0.4.
3- Protein greater than 200 mg/dl.
4- WBC greater than 1000/μL.
5- Greater than 80% polymorph nuclear neutrophils.

CSF findings suggestive of viral meningitis are:

1- WBC counts fewer than 300 cells per mm3.
2- Less than 20% of which are neutrophils.
3- Normal protein and glucose levels.
4- HSV encephalitis: may be increased RBCs (temporal lobe hemorrhage).

Reasons for a lack of classic CSF findings in bacterial meningitis:

1- Partially treated meningitis (e.g., prior antibiotics).
2- Time of LP (is it early in course of the disease before the patient mounts a response, or late in the course?): Thus, the typical CSF findings may not be present in every patient who has bacterial meningitis and may even show a normal WBC in the CSF and/or lymphocyte predominance, especially if early in the disease

	Normal adult	Normal child	Normal term infant	Normal preterm infant
WBC (per μL)	<5	0–7	8 (0–22 range)	9 (0–25 range)
WBC type	All monos	0% polys	61% polys	57% polys
Glucose (mg/dL)	>40	40–80	52 mean (34–119 range)	50 mean (24–63 range)
Glucose ratio (cerebrospinal fluid/blood)	>0.4	>0.5	0.44–1.28	0.55–1.05
Protein (mg/dL)	<50	5–40	90 mean (20–170 range)	115 mean (65–150 range)

Agent	Opening Pressure (mmHg)	WBC count per μL	Glucose (mg/dL)	Protein (mg/dL)	Microbiology
Bacterial Meningitis	200-300	100-5000; >80% PMNs	<40	>100	Specific pathogen demonstrated in 60% of Gram stains and 80% of cultures
Tuberculous Meningitis	180-300	100-500; lymphocytes	Reduced, <40	Elevated, >100	Acid-fast bacillus stain, culture, PCR
Viral Meningitis	90-200	10-300; lymphocytes	Normal, reduced in LCM and mumps	Normal but may be slightly elevated	Viral isolation, PCR assays
Aseptic Meningitis	90-200	10-300; lymphocytes	Normal	Normal but may be slightly elevated	Negative findings on workup
Normal values	80-200	0-5; lymphocytes	50-75	15-40	Negative findings on workup

Treatment

1- Initial management:

- Empiric antibiotics must be started immediately, even before the results of the lumbar puncture and CSF analysis are known
- Empirical therapy may be chosen on the basis of the age of the patient, whether the infection was preceded by head injury, whether the patient has undergone neurosurgery and whether or not a cerebral shunt is present
- For instance, in young children and those over 50 years of age, as well as those who are immunocompromised, addition of ampicillin is recommended to cover Listeria monocytogenes

Predisposing factor	Antimicrobial therapy
Age 0-4 wk	Ampicillin plus cefotaxime; or ampicillin plus an aminoglycoside
Age 4-12 wk	Ampicillin plus a third-generation cephalosporin**
Age 3 mo to 18 yr	Third-generation cephalosporin; or ampicillin plus chloramephenicol
Age 18-50 yr	Third-generation cephalosporin***
Age > 50 yr	Ampicillin plus a third-generation cephalosporin
Immunocompromised state	Vancomycin plus ampicillin plus ceftazidime
Basilar skull fracture	Third-generation cephalosporin
Head trauma	Vancomycin plus ceftazidime
Post neurosurgery or CSF shunt	Vancomycin plus ceftazidime

*****Vancomycin should be added to empirical therapeutic regimens when highly penicillin- or cephalosporin-resistant strains of S. pneumonia are suspected.

** Cefotaxime or ceftriaxone.

*** Add ampicillin if meningitis caused by L. monocytogenes is suspected.

Antibiotic	Total daily dose		Dose interval
	Child > 3 months	Adult	
Ampicillin	200 mg/kg/day	12 gm/day	4-6 hrs
3rd generation cephalosporin	100-200 mg/kg/day	6-12 gm/day	4-6 hrs
Vancomycin	60 mg/kg/day	2 gm/day	6-12 hrs
Metronidazole	30 mg/kg/day	1.5–2 gm/day	6-8 hrs

2- Specific antimicrobial therapy

- For an antibiotic to be effective in meningitis, it must not only be active against the pathogenic bacterium, but also reach the meninges in adequate quantities; some antibiotics have inadequate penetrance and therefore have little use in meningitis
- The results of the CSF culture generally take longer to become available (24–48 hours). Once they do, empiric therapy may be switched to specific antibiotic therapy targeted to the specific causative organism and its sensitivities to antibiotics

3- Duration of therapy:

- It must be emphasized that guidelines regarding the duration of therapy are not standardized and that the duration of therapy may need to be individualized on the basis of the patient's clinical response

Microorganism	**Duration of therapy, days**
Neisseria meningitidis	7
Haemophilus influenzae	7
Streptococcus pneumonia	10–14
Streptococcus agalactiae	14–21
Aerobic gram-negative bacillia*	21
Listeria monocytogenes	>21

* Duration in the neonate is 2 weeks beyond the first sterile CSF culture or >3 weeks, whichever is longer.

4- Dexamethasone therapy

- Indications:
  - Recommended in infants/children older than 6 weeks with H influenzae B meningitis
  - Infants and children older than 6 weeks who have pneumococcal meningitis
  - Adults who have proven or suspected pneumococcal meningitis
- Bebefits:
  - Corticosteroids are life saving in severe cases of bacterial meningitis.

- They help to decrease brain oedema, decrease platelet aggregation and improve suprarenal function
- Prevents sequelae as deafness, hydrocephalus

- Regimen:
  - Dexamethasone was given either 15 minutes before or simultaneously with antibiotics and continued every 6 hours for 4 days **(40 mg/day i.v.)**
- The reason why it is recommended that dexamethasone be given 15 to 20 minutes before administering antibiotics:
  - Is that dexamethasone inhibits the release of IL-1, TNF, and other inflammatory cytokines by microglia and macrophages only if it is given before these cells are activated by the endotoxins released from the killing of bacteria. Once these cells have been induced to produce these inflammatory cytokines, dexamethasone does not affect cytokine (IL-1, TNF, others) production by the body's cells (macrophages, glial cells, and others)
- Precaution:
  - Vancomycin penetration into the CNS is mainly dependent upon meningeal inflammation. Dexamethasone, probably because it decreases meningeal inflammation, significantly lowers therapeutic drug levels in the CSF.
  - Thus, a concern has been raised regarding vancomycin efficacy when given with dexamethasone, so some recommend adding rifampin whenever there is concurrent administration of vancomycin and dexamethasone

5- Reduction of intracranial pressure [if > 15-20 mmHg]

- Elevation of the head of the bed to 30 degrees to maximize venous drainage with minimal compromise of cerebral perfusion.
- Intubation and hyperventilation to maintain the $PaCO_2$ between 27 and 30 mmHg, which causes cerebral vasoconstriction and a reduction in

cerebral blood volume. Reduction to 20 or below should be avoided to prevent resultant cerebral ischemia. Hyperventilation becomes less effective with duration of use and may have little effect after 48 hours of use.

- Use of hyperosmolar agents (e.g. mannitol) to make the intravascular space hyperosmolar to the brain and permit movement of water from brain tissue into the intravascular compartment.
- Corticosteroids.

6- Surgery

- Hydrocephalus may require insertion of a temporary or long-term drainage device, such as a cerebral shunt
- Congenital or acquired cranial defects and dermal sinuses causing recurrent meningitis
- Basilar skull fracture having persistent dural defects with CSF leak causing recurrent episodes of bacterial meningitis

7- General measures

- If meningococcal disease is suspected in primary care, guidelines recommend that benzyl penicillin be administered before transfer to hospital
- Intravenous fluids should be administered if hypotension or shock is present
- Admission to an intensive care unit if deemed necessary
- Mechanical ventilation may be needed if the level of consciousness is very low, or if there is evidence of respiratory failure
- Seizures are treated with anticonvulsants

Patients with possible intracerebral abscess should receive metronidazole to cover anaerobes as well as chloramphenicol

Prevention

1- Vaccination

- All three major pathogens of meningitis can be prevented by vaccines
- These vaccines require an intact cold chain of refrigeration (< 5º C) at all stages of transport
- Indications (for high-risk group):
    - Individuals > 65 years of age
    - Patients with chronic cardiovascular, pulmonary, liver disease &diabetes mellitus
    - Patients with sickle cell disease
    - Patients with functional asplenia or those who have had a splenectomy
- Drawbacks of vaccines:
    - Less immunogenic in infants < 2 years (high-risk group).
    - Induced immunity is T-cell dependent that is relatively short-living, with antibody titers decreasing after 3 years following a single dose of the vaccine
    - There is no vaccine for serogroup B meningococci

2- Chemoprophylaxis

- It is used to prevent secondary cases of H. influenzae and N. meningitidis
- It is indicated for close contacts only
- Secondary cases generally occur within 6 days of an index case of H. influenzae and within 5 days of an index case of N. meningitidis meningitis
- Regimen for meningococcal meningitis:
    - **Rifampin** given in a 600 mg dose for adults, 10 mg/kg every dose for children older than 1 month, 5 mg/kg every dose for neonates (age less than or equal to 30 days) orally every 12 hours for a total of four doses.

- Those receiving chemoprophylaxis should be counseled to watch for fever, rash, or any other meningeal signs or symptoms.
- Alternative single-dose chemoprophylaxis regimens are **ciprofloxacin** 500 mg by mouth for adults and **ceftriaxone** 250 mg intramuscularly (age greater than or equal to 12 years) or 125 mg intramuscularly (age less than 12 years)

- Regimen for H.influenza meningitis
  - **Rifampin** is warranted for non pregnant household contacts if there are young children (age younger than 4 years) in the household. The by mouth dose is 600 mg for adults and 20 mg/kg for children once daily for 4 days.
- Chemoprophylaxis is not given for pneumococcal meningitis

Aseptic meningitis

Definition

1- The term aseptic meningitis refers loosely to all cases of meningitis in which no bacterial infection can be demonstrated

2- CSF is usually clear & shows an increase of cells mainly mononuclear cells, with no bacterial growth on culture

Etiology

Infectious group

1- Viral meningitis :

- Enteroviruses: such as coxsackie and echoviruses, comprise more than 80% of all episodes of aseptic meningitis and are the most commonly identified causes of CNS viral infections
- Herpes simplex virus type 2 (and less commonly type 1).
- Varicella zoster virus (known to cause chicken pox and shingles).
- Mumps virus.
- HIV (Human immunodeficiency virus).

- LCMV (lymphocytic choriomeningitis virus).
- Adenoviruses, influenza types A and B, and Epstein-Barr virus
- Cytomegalovirus
- Rabies, rubella.
- West Nile virus.
- Poliomyelitis virus

Predisposing factor	Common viral agents
All patients	Enteroviruses**,** Herpes simplex viruses**,** Varicella zoster virus**,** HIV virus, Epstein-Barr virus.
Unvaccinated/incomplete vaccination course	Mumps virus.
Immunocompromised host	Cytomegalovirus.
Travel history	West Nile virus (America, Africa**,** West Asia, Australia , Mainland Europe) Saint Louis encephalitis virus (United states)**.** Tick-born encephalitis virus (Mainland Europe and Asia).
Contact with rodents droppings or urine	Lymphocytic choriomeningitis virus**.**

2- Some conditions of bacterial meningitis:

- Mycoplasma pneumonia
- Chlamydia spp.
- Rickettsia spp.
- Early stage of tuberculous meningitis
- Septic meningitis: treated cases or very early stage

3- Spirocheatal

- Leptospira icterohemorrhagica
- Acute syphilitic meningitis
- Lyme disease

4- Mycotic

- Histoplamsosis
- Cryptococcosis
- Coccidomycosis

5- **Protozoal**

- Amoebic such as Naegleria fowleri contracted from fresh water sources
- Toxoplasmosis
- Malignant malaria

6- **Helminthic**

- Angiostrongylus cantonensis
- Gnathostoma spinigerum
- Trichinosis
- Schistosoma japonicum
- Conditions such as cysticercosis, toxocariasis, baylisascariasis and paragonimiasis

Post infectious group

1- **Vaccinations** as rabies, MMR vaccines

2- **Natural infections**

- As varicella, rubella and mumps
- Measles and mumps aseptic meningitis may occur before the appearance of rash or glandular enlargement. Serological tests are important

Non infectious group

1- **Drug induced**

- Mainly non-steroidal anti-inflammatory drugs especially ibuprofen,
- Antibiotics especially cotrimoxazole
- Intravenous immunoglobulins and intrathecal agents
- Other agents reported less frequently include carbamazepine, azathioprine, anti-CD3 monoclonal antibodies

2- **Malignant meningitis**

- Meningeal carcinomatosis (MC) is the malignant infiltration of the meninges from a distant solid tumor, most commonly adenocarcinoma of the breast or lung and melanoma**.** MC also has been described infrequently in association with colon cancer

- Lymphoma

3- **Meningeal irritation from contagious focus**

- Parameningeal septic focus as chronic mastoiditis, sinusitis, cerebral abscess and subdural abscess
- Thrombophlebitis of cerebral veins as cavernous, lateral and superior sagital veins
- Granuloma
- Hematoma
- Tumor

4- **Sarcoidosis, systemic lupus erythematosus** and vasculitis such as Behcet's disease may cause meningitis

5- **Epidermoid cysts and dermoid cysts**: may cause meningitis by releasing irritant matter into the subarachnoid space

6- **Rheumatologic disorders**, such as Sjogren's syndrome

7- **Allergy** as serum sickness

8- **Blood diseases** as leukemia

9- **Toxins or irritants**

- Exogenous as lead, arsenic or lipoidol
- Endogenous as diabetic or uraemic coma

10- Demyelinating diseases as acute necrotizing haemorrhagic encephalomyelitis

11- Mollaret's meningitis: is a syndrome of recurrent episodes of aseptic meningitis, it is now thought to be caused by herpes simplex virus type 2

Clinical features

1- Fever, headache, vomiting

2- **Signs of meningeal irritation** including stiffness of the neck

3- Frank signs of motor or sensory impairment are absent

4- **Drowsiness, confusion** and rarely convulsions or coma may supervene

Diagnosis

1- **Lumbar puncture** → see table before (CSF is clear, no bacterial growth).

2- **Diagnosing viral meningitis**

Cause	Key diagnostic test	Other potentially useful tests
Enteroviruses	CSF PCR*	Throat and rectal swabs—culture, PCR (positive for longer than CSF)**.**
Herpes simplex virus (HSV	CSF PCR*	HSV type specific serology. Detection in genital lesions—PCR, culture, immunofluorescence, electron microscopy, Tzanck smear
Varicella zoster virus	CSF PCR*	Detection in skin lesions—PCR, culture, immunofluorescence, electron microscopy, Tzanck smear
HIV	Serology*	Serial IgG or combined IgG and antigen tests— seroconversion? HIV viral load (plasma, CSF)
Mumps	Serology (serum, oral fluid**)**	PCR (throat swab, urine, EDTA blood, oral fluid
Epstein-Barr virus (EBV)	EBV specific serology, VCA IgM and IgG, EBNA IgG	CSF PCR. Monospot test

Treatment

1- Treatment of the cause

2- **Mild cases of viral meningitis** can be treated at home with conservative measures such as fluid, bed rest, and analgesics

3- **In suspected herpes simplex virus infection:**

- Acyclovir, 10 mg/kg given every 8 h (may use up to 20 mg/kg every 8 h for children under age of 12 years)
- The International Herpes Management Forum (IHMF) recommends that all patients with herpes simplex encephalitis should receive intravenous acyclovir for 14-21 days

4- Treatment of parasitic meningitis → ®

5- Treatment of neurosyphilis → crystalline penicillin IV

6- Treatment of rickettsia → doxycycline

Chronic meningitis

Causes

1- TB meningitis
2- Fungal meningitis (Cryptococcus)
3- Sarcoidosis
4- Leukemia
5- Lymphoma
6- Brain tumors
7- Metastasis to the brain

Lumbar puncture

Indications of CSF analysis in general

1- Viral and bacterial infections, such as meningitis and encephalitis.
2- Tumors or cancers of the nervous system.
3- Syphilis, a sexually transmitted disease.
4- Bleeding (hemorrhaging) around the brain and spinal cord.
5- Multiple sclerosis, a disease that affects the myelin coating of the nerve fibers of the brain and spinal cord.
6- Guillain-Barré syndrome, an inflammation of the nerves.

Contraindications

1- Children with hypotension, respiratory distress or cardiac disorder: as the positioning for L.P can further compromise ventilation and blood flow, so this procedure is deferred until the child's condition is stable.
2- Profound thrombocytopenia or a clotting disorder: the L.P should be delayed until the condition is corrected.
3- Any patient who manifests fever and evidence of increased intracranial pressure or focal neurologic deficit: should undergo an imaging study before L.P to exclude a brain abscess or mass lesion.

4- Cellulites or abscess of the skin overlying the lumbar vertebrae.

5- In all these situations empirical therapy is begun without delay.

Manifestations of ↑ ICT

1- Headache

2- Vomiting without nausea

3- Ocular palsies

4- Altered level of consciousness

5- Back pain

6- Papilledema.

- If papilledema is protracted, it may lead to visual disturbances, optic atrophy, and eventually blindness.

7- If mass effect is present with resulting displacement of brain tissue, additional signs may include:

- Pupillary dilatation
- Abducens palsies
- The Cushing's triad. Cushing's triad involves an increased systolic blood pressure, a widened pulse pressure, bradycardia, and an abnormal respiratory pattern.

8- In children, a slow heart rate is especially suggestive of high intracranial pressure

Technique of L.P

1- **Position:**

- For diagnostic lumbar puncture, the left lateral recumbent position (for right-handed physicians) is preferred.
- Ill patients are generally unable to sit up and the sitting position increases the risk of headaches post-puncture, probably because the CSF pressure and flow is higher than in the lateral recumbent position**.**
- In the lateral recumbent position, the patient should be positioned with the back flexed as far as possible. Ask the patient to try to touch the flexed knees with his/her chin**.**

- In preterm infants, the preferred position is the sitting or "lateral recumbent without knees-to-chest position," which results in less hypoxemia than the "lateral recumbent knees-to-chest position." The neck is best maintained in the neutral position.

2- <u>Determine Site of Insertion:</u>

- A line joining the most superior part of both iliac crests (Tuffier's line) will intersect the midline at the L4 spinous process or L4/L5 interspace**.**
- The needle is inserted at the L3/L4 or L4/L5 interspace**.**
- Both these spaces are below the termination of the spinal cord at L1/L2 in the majority of adults**.**
- The L4/5 or L5/S1 interspace should be used in children as the spinal cord ends at L3

3- <u>Infiltrate:</u> Infiltrate local anesthetic only subcutaneously

4- <u>Insert Needle</u>:

- Insert the needle at the superior aspect of the spinous process that lies inferior to the space to be entered. Aim for the umbilicus (15° cephalad)**.**
- Never aspirate with a syringe as a small amount of negative pressure can cause subdural hemorrhage or herniation.
- The amount of CSF collected for diagnostic purposes should be restricted to the smallest volume necessary. For children this is typically 0.5 ml/ tube and not more than 3 ml in total

Side effects

1- Post L.P headache.

2- Local back pain.

3- Bleeding from the spinal needle insertion (Traumatic tap).

4- Brain herniation.

5- Dry tap.

6- Intraspinal epidermoid tumour.

7- Pain referred to the lower limb (due to nerve root injury).

8- Retroperitoneal abscess (very rare).

Signs of herniation

1- Bradycardia and abnormal respiratory patterns.

2- Unequal or dilated non reactive pupils.

3- Skew deviation or dysconjugate eye movements.

4- Decorticate or decerebrate posturing

A traumatic tap should be distinguished from a subarachnoid hemorrhage.

Fluid generally clears after the first and second tubes in a traumatic tap. The presence of a clot in one of the tubes strongly favours a traumatic tap. Clotting does not occur in a subarachnoid hemorrhage due to defibrinated blood being present in the CSF

Brucellosis (Malta fever)

Causative organism

1- **Brucella spp.** → Gram –ve non-spore forming coccobacilli

2- The organism is **intracellular** and can remain hidden in RES, despite this brucellosis not common and not severe in HIV patients

3- The organism is found in the **uterine discharge and milk** of infected animals

4- There are **3 important species**

- Brucella melitensis:
  - The most virulent and invasive
  - Usually affecting goats and sheep, but also found in camels
  - Distribution → around Mediterranean, middle east and central and south America
- Brucella abortus
  - Usually a disease of cattle → abortion
  - Distribution → Africa and india
- Brucella suis
  - A disease of pigs
  - Distribution → USA

5- **Infected animal**

- May appear symptomless or
- Epididymitis, abortion and infertility may occur

Mode of transmission

1- **Ingestion:**

- Unpasteurised milk or milk products of infected animals including soft cheeses
- Acidified milk products (e.g. yoghurt, buttermilk الزبدة) are less hazardous but still pose a risk

2- **Inhalation:**

- Aerosol contact, particularly with infected products of conception from animals
- Aerosol release from laboratory accidents or in abattoirs المدابح

3- **Direct contact or inoculation:**

- Entry via the conjunctiva, usually in veterinarians or farmers
- Entry through skin abrasions

- Veterinarians using live attenuated vaccine (B. abortus S19 and B. abortus RB51)
- Rarely, blood transfusion, bone marrow/organ transplant, sexual, transplacental, via breast milk

N.B. Eating meat does not transmit brucellosis, except if eaten raw and has been externally contaminated

Risk factors → occupational disease, common in

1- Farmers

2- Meat handlers

3- Veterinary services

Clinical features

1- Incubation period

- About 5-30 days, but may up to 6-12 months
- The infection may persist for months without causing any symptoms

2- Clinical features can be diverse and the **course of the disease is variable**

3- Acute brucellosis

- **The major features are:**

  - Prolonged fever [FUO]: recurrent prolonged bouts of fever that is worse at night. If specific treatment is not given, undulating patterns of fever may last for several weeks (3-4wks), followed by an afebrile period and then relapse
  - Debilitation, depression and lethargy
  - Weight loss
  - Muscle and joint pain (generalized body aches esp. low backache) [focal musculoskeletal symptoms occur in 50% of cases and may be the only clue that differentiates brucellosis from other causes of fever as typhoid fever, Q fever or malaria]
  - Profuse Sweating is often present.
  - Rigors
  - Anorexia, malaise and headache

- **Epistaxis** is an unusual but well recognized presentation because of the associated thrombocytopenia, but hematemesis and melena are very unusual
- **Dry cough** but with clear chest often present, mimicking the presentation of typhoid
- **Mild to moderate splenomegaly or HSM** → present in 1/4 of cases
- **Cervical or other lymphadenopathy** → present in up to 10% esp with B. abortus, and must be differentiated from glandular fever, HIV or tuberculous
- **Outcome**
    - Acute disease lasts for weeks, leading to chronic, relapsing infection that may last for years
    - A substantial minority will only have self-limiting disease

4- **<u>The pattern of presentation</u>** varies with the age of the patient and the infecting species

- **Brucella abortus**
    - More insidious onset
    - More likely to become chronic
    - More likely to affect the axial skeleton
- **B. melitensis**
    - More acute onset
    - More severe disease
    - More likely to affect peripheral joints as well as the vertebrae
- **B. suis**
    - Acute presentation complicated by focal deep tissue abscesses
- **Children**
    - Often present with fever and a single affected joint typically the hip or knee (may be mistaken for rheumatic fever or septic arthritis)

5- **Chronic brucellosis**

- **Onset** is insidious
- There is a **story** of recurrent flu with lassitude,malaise, headache, sweating, low backache and depression
- **Temperature** may be normal
- **The appearance** may reflect a serious disease or may be normal
- Moderate **splenomegaly** may be present

Complications

[May occur with acute or chronic disease and may be the presenting feature]

1- **Bone and joints:**

- **Incidence**
  - Osteoarticular complications are the most common focal forms of the disease
  - Reported in 10-80% of cases depending on the ages of the patients & Brucella spp.
- **Sacroiliitis** occurs in young patients → local tenderness on movement of the sacroiliac joints
- **Spondylitis**
  - Occurring in old persons (average age is 40 yr)
  - May affect single or multiple sites
  - Usually in the lumbar spine (L 4) → local tenderness
  - Causing bone necrosis with new bone formation (sclerosis), and can destruct vertebra and disc
- Paravertebral, epidural, or psoas **abscesses** may occur
- **Arthritis**
  - Usually involves large weight-bearing joints (hips and knees), may be acute or chronic
  - Reactive → commonly polyarticular, migratory resembles rheumatic fever **or**
  - Septic → usually monoarticular

- Signs of arthritis include swelling, hotness, tenderness and effusions of the affected joint

- **Osteomyelitis:** rare, affecting long bones as femur, tibia and humorous
- **Deformity of the back or long tract neurological signs** are very unusual and suggest TB rather than brucellosis

2- <u>Neuro-psychiatric:</u>

- **Depression** and mental inattention are common symptoms ± psychosis.
- Neurologic syndromes in brucellosis (**Neurobrucellosis**) occurs in about 5% of cases and include:
    - Meningitis, meningoencephalitis
    - Myelitis, radiculoneuronitis
    - Brain abscess, epidural abscess
    - Granuloma
    - Demyelinating and meningovascular syndromes.
- **Acute or chronic meningitis** is the most frequent nervous system complication.

3- <u>Cardiovascular:</u>

- **Endocarditis** occurs in 1- 2% of cases esp. with B. melitensis, but it accounts for the majority of brucellosis-related deaths (valve destruction and heart failure).
- Pericarditis, myocarditis are also reported.

4- <u>Genitourinary:</u>

- Interstitial nephritis, pyelonephritis, glomerulonephritis & IgA nephropathy have been reported.
- **Epididymoorchitis** occurs in 5-10% of men with brucellosis (must be distinguished from mumps).
- Unilateral or bilateral epididymoorchitis common in children
- Prostatitis and seminal vesiculitis common in adults

5- Gastrointestinal:

- **Hepatitis** with mild jaundice (non-specific or granulomatous disease)
- Hepatosplenic abscesses are rare
- Mesenteric lymphadenitis with abscess formation
- Ulceration, bleeding & perforation.
- Acute ileitis, colitis and spontaneous peritonitis
- Lesions ranging from small, almost insignificant aggregates of mononuclear cells surrounding foci of necrosis, to a diffuse nonspecific inflammation resembling viral hepatitis.
- Acute cholecystitis or Gall stones.

6- Cutaneous

- Petechiae, purpura, and vasculitis are reported in 5% of patients.

7- Pulmonary: rare

- Airborne transmission of brucellosis is a problem in abattoirs and laboratories.
- Complications range from flu-like symptoms to bronchitis, pneumonia, lung nodules, abscess, military lesions, hilar adenopathy, pleural effusion or empyema.

8- Hematologic:

- Anemia, leukopenia, thrombocytopenia, and clotting disorders.
- Granulomas are found in the bone marrow in as many as 75% of cases.

9- Ocular:

- Iridocyclitis, nummular keratitis, multifocal choroiditis & optic neuritis and uveitis have been reportd.

10- Pregnancy → abortion.

Diagnosis

1- CBC

- Shows low WBCs with lymphopenia and mild thrombocytopenia
- Occasionally, there is more pronounced reduction of platelets and Hb

2- ALT, AST, ALP → mild elevation is common

3- Culture [the most reliable method for confirming diagnosis]

- Blood culture
  - + ve in 2/3 of cases of B. melitensis & < 1/3 of B. abortus cases
  - Most of the positives ocuuring between days 7 and 21, but may take up to 6 weeks if modern culture systems not used
  - Laboratory staff must be told that brucellosis is a possibility, both to be aware of the hazard of aerosol spread and to prolong the culture period
- Single bone marrow culture
  - Has a better yield than 3 sets of blood cultures
  - Occasionally useful in case of –ve blood culture (preceding antibiotics)
- Synovial fluid culture → should be done in any case of septic arthritis in endemic areas
- Aspirates or biopsies from L.N. ,liver or bone → can be cultured and may containing non-caseating granulomas which can't be easy distinguished from TB granulomas
- CSF → usually shows mild ↑ of lymphocytes and proteins, and organisms may be cultured

4- X-ray images هام

- Bone changes are seen later in the disease
- Typically, erosions at the edge of joints or the end plates of vertebrae, with associated sclerosis
- Marked bony destruction is unusual and is more suggestive of TB

5- **Isotope bone scans** هام

- Hotspots in affected bones and joints
- Frequently reveal further foci of infection that are asymptomatic

6- **Clinical and radiological features that discriminate** between spine involvement in TB and brucellosis هام

	Brucellosis	Tuberculosis
Site	Lumbar + others	Dorsolumbar
Vertebrae	Multiple or contiguous	Contiguous
Discitis	Late	Early
Body	Intact until late	Morphology lost early
Canal compression	Rare	Common
Epiphysitis	Anterosuperior (Pedro-Pons' sign)	General : upper + lower disc region, centre, subperiosteal
Osteophyte	Anterolateral (parrot beak)	Unusual
Deformity	Wedging uncommon	Anterior wedge (gibbus)
Recovery	Sclerosis of the whole body	Variable
Paravertebral abscess	Small, well localized	Common + discrete loss transverse process
Psoas abscess	Rare	More likely

7- **U/S, echocardiography and ophthalmological examination** → for other complications

8- **Standard agglutination test**

- **Value:** the most common method used for making the diagnosis
- **Principle :** brucella antigen supplied with the kit is added to successive dilutions of the patient serum, and if visible agglutination occurs (due to antibodies in the patient's serum), the test is +ve
- **Precution :** this test is affected by the prozone phenomenon, which causes false –ve results because patients with brucella have IgA antibodies, which interfere with agglutination by IgG or IgM at low dilutions, and the blocking effect is only overcome at increasing serum dilutions
- **Recommendation:** a wide range of dilutions of the patient's serum (1/20 – 1/5120) is a must to avoid the prozone phenomenon

- **Interpretation**
    - 4-folds rise of the titre between acute and convalescent samples (10-14 days) → is diagnostic [but too delayed to guide immediate treatment]
    - In endemic areas or with occupational risk → a titre of 1/160 or 1/320 or more is diagnostic [these patients have already a low titres of antibodies, so the diagnostic cut-offs for a single sample to be +ve have to be set higher]
    - In non-endemic areas → a titre of 1/80 is strongly predictive
- **False –ve results may occur**
    - In about 10% of culture +ve cases (seronegative brucellosis) or
    - If low dilutions are used
- **False +ve results may occur with**
    - Gram negative bacteria (Yersinia, cholera)
    - Recent cholera immunization
- **Prediction of chronic infection**
    - Mercaptoethanol can be added to patient's serum to dissociate IgM and therefore indicate if IgG predominates which is more suggestive of chronic infection, but this is only moderately reliable
- **Coomb's antiglobulin test**
    - May be used to detect the non-agglutinating IgA"blocking antibodies" that appear during the subacute stage of infection [has replaced by ELISA]
- **N.B.** there is cross reaction between B. abortus and melitensis, so serology alone can't reliably distinguish between these infections

9- ELISA → detect IgG, IgM or IgA (sensitive but not widely used)

10- PCR for DNA and urinary dipsticks for antibodies → sensitive but not widely used

11- Rose Bengal test (rapid slide agglutination test)

- Designed for animals screening and diagnosis
- Used as screening test on humans in many tropical areas but have not been fully validated for this purpose

Treatment

1- There are 3 questions guide the management

- Is the disease acute (duration < 1month) or relapsing or chronic (> 6 months)
- Is there focal disease of bone or joints or other complications?
- Has TB definitely been excluded?

2- Duration of treatment

- Adults with acute non-focal disease → 6 weeks
- Children < 12 yr with acute non-focal disease → 6 weeks but 3 weeks may be adequate
- Patients with focal disease and/or chronic disease → 3 months

3- Principles of treatment

- Monotherapy should not be used because, although clinical illness responds in short time, early relapse occurs in > 30% of cases
- Combination of 2 antibiotics is the preferred regimen
- Triple therapy is indicated in complicated cases
- In patients in whom TB has not been excluded
    - Use antimicrobials to which only brucellosis responds (i.e. don't use streptomycin or rifampicin) **or**
    - Treat both infections simultaneously

4- The gold standard regimen

- **Doxycycline** 100 mg twice daily for 6-12 week + **streptomycin** 1 g I.M. daily for 2-3 weeks [the long period for chronic cases]
- Relapse rate after this regimen only 5%

5- <u>Alternative regimens</u>

- **Doxycycline** 100 mg twice daily + **rifampicin** 600 mg once daily before breakfast [Relapse rate after this regimen > 10%]
- **Doxycycline** 100 mg twice daily + **Co-trimoxazole** 3 tab. Twice daily + folic acid daily [can cause anemia and drug rashes]
- Rifampicin can interact with the contraceptive pill and therefore other forms of contraception may be necessary

6- <u>Children < 12 yrs</u>

- Rifampicin + Co-trimoxazole

7- <u>Pregnancy</u>

- Rifampicin alone or
- Rifampicin + Co-trimoxazole 2 tab. Twice daily [in the 1st trimester, avoid co-trimoxazole or add folic acid supplements]
- Doxycycline is contraindicated in pregnancy and lactation

8- <u>Complicated cases</u> [spondylitis, endocarditis, meningitis]

- Doxycycline + rifampicin + gentamicin
- Ceftriaxone may be added
- Patients with endocarditis often need valve replacement

9- <u>Other drugs</u>

- Some add fluoroquinolones as a 3rd drug in difficult complicated cases or as a substitute for doxycycline in pregnant women
- Azithromycin is not useful

- **Acute cases** → 2 drugs for 6 weeks
- **Chronic or relapsing cases** → 2 drugs for 3 months
- **Complicated cases** → 3 drugs for 3 months

Follow up

1- Follow-up is essential **at 3 and 6 weeks** to encourage patient adherence to the chemotherapy regimen.

2- Further follow-up **at 3 months, 6 months and 1 year** is the minimum to detect relapse

3- **The main indicators of success are:**

- Improvement in general mood and health
- Return of appetite and weight
- Absence of fever
- Disappearance of any positive findings at presentation eg: lymphadenopathy, hepatosplenomegaly

4- **Serology**

- Not useful for follow up as decline of antibody levels is slow over months to years after successful treatment
- Not predictably ↑ to warn that relapse is imminent

5- **Repeat blood cultures** are not necessary unless there is suspicion of relapse or failure

6- **Relapse**

- Defined as a further episode of brucellosis occurring < 6 months after the first
- The cause is antibiotic incompliance rather than drug resistance
- Treatment: 2 drugs for 3 months [some include streptomycin to be sure that the drugs have been taken]

7- **Immunity** after brucellosis is not solid

Salmonella infections

Forms of infection

1- Acute enteric fever

2- Acute gastroenteritis (food poisoning)

3- Chronic salmonellosis: endemic in Egypt in bilharzial patients

4- Septicemia

5- Metastatic lesions e.g. osteomyelitis, liver abscess, brain abscess

6- Asymptomatic carrier state

Typhoid fever

Etiology and pathogenesis

1- Causative organisms in Egypt:

- S. typhi → 80 % of cases
- Salmonella paratyphi A → 20% of cases

2- Organisms

- Gram negative bacilli of the enterobacteriacae
- All posses somatic O and flagellar H antigens
- S.typhi and paratyphi C posses a surface Vi antigen that coats the O antigen and potentially protects it from antibody attack

3- Mode of transmission [Fecal-oral]

- Ingestion of contaminated water, food or milk with feces or urine of a case or carrier through food handler or flies
- The main source of infection
    - Chronic carriers
    - Asymptomatic convalescent carriers

4- Risk factors

- *S typhi* are able to survive a stomach pH as low as 1.5. So, any condition decrease stomach acidity can facilitate *S typhi* infection as
  - Antacids
  - H2 blockers and PPIs
  - Gastrectomy, achlorhydria and chronic gastritis
- Various genetic polymorphisms
- Environmental and behavioral risk factors
- The many zoonotic salmonellas, which usually cause gastroenteritis, occasionally cause an enteric fever-like illness esp. in patients with HIV

5- Pathogenesis

- In stomach → most of the organisms are killed by gastric acidity
- In small intestine → the organism multiply in payers patches (mesenteric lymph nodes) then passes to the blood stream causing 1ry bacteraemia that persists for 1 week (during the I.P)
- The bacteria is taken up by R.E.S (liver, gall bladder, spleen, kidney and bone marrow), where it multiply and then passes to the blood causing a 2nd heavier bacteremia that concides with fever and clinical illness
- In the gall bladder → the organism may stay and causing chronic carrier

Clinical features

Classic typhoid fever syndrome

1- Incubation period: 7-21 days (average: 2 weeks) after ingestion of *S typhi.* but usually shorter in paratyphoid fever

2- Age : more common in children and young adults (2-35yr)

3- The fever: [the only almost constant symptom]

- Is stepwise, characterized by a rising temperature over the course of each day [often with evening rise] that drops by the subsequent morning. The peaks and troughs rise progressively over time.
- Onset usually gradual
- Rigors are unusual

4- The first week:

- The notorious gastrointestinal manifestations of the disease develop
    - Diffuse abdominal pain and tenderness and, in some cases, fierce colicky right upper quadrant pain.
    - Constipation that lasts the duration of the illness (Monocytic infiltration inflames Peyer patches and narrows the bowel lumen)
- The individual then develops
    - Dry cough
    - Dull frontal headache
    - Anorexia and generalized bony aches
    - Delirium and an increasingly stuporous malaise.
- At the end of the first week, the fever plateaus at 39-40°C.

5- The second week:

- The patient develops rose spots
    - Which are pink or salmon-colored, blanching, maculopapules usually 1-4 cm wide and < 5 in number, mainly on the trunk
    - Only seen with ease in fair-skinned patients
    - Generally resolve within 2-5 days.
    - These are bacterial emboli to the dermis and occasionally develop in persons with shigellosis or nontyphoidal salmonellosis.
- The signs and symptoms listed above progress.
- Abdominal distention
- Soft splenomegaly is common (often tender) or even hepatomegaly.
- Relative bradycardia
- Dicrotic pulse (double beat, the second beat weaker than the first) may develop.

6- **The third week:**

- The patient becomes more toxic and anorexic with significant weight loss.
- Conjunctival infection
- Tachypnea with a thready pulse
- Crackles over the lung bases.
- Abdominal distension is severe.
- Some patients experience foul, green-yellow, liquid diarrhea (pea soup diarrhea).
- The individual may descend into the typhoid state, which is characterized by apathy, confusion, and even psychosis.
- Necrotic Peyer patches may cause bowel perforation and peritonitis. This complication is often unheralded and may be masked by corticosteroids. At this point, overwhelming toxemia, myocarditis, or intestinal hemorrhage may cause death.

7- **The fourth week:**

- The fever, mental state, and abdominal distension slowly improve over a few days.
- Intestinal and neurologic complications may still occur in surviving untreated individuals.
- Weight loss and debilitating weakness last months.
- Some survivors become asymptomatic *S typhi* carriers and have the potential to transmit the bacteria indefinitely.

Atypical presentations of typhoid fever

1- The stepladder fever pattern now occurs in 12% of cases only. In most presentations, the fever has a steady insidious onset.

2- Young children, AIDS, and 1/3 of immunocompetent adults, develop **diarrhea** rather than constipation.

3- **Atypical manifestations** of typhoid fever include:

- Isolated severe headaches that may mimic meningitis

- Acute lobar pneumonia
- Isolated arthralgias
- Urinary symptoms
- Severe jaundice
- Fever alone
- Some patients, present primarily with neurologic manifestations such as delirium or, in extremely rare cases, parkinsonian symptoms or Guillain-Barré syndrome.

Treated typhoid fever

1- If appropriate treatment is initiated within the first few days, the disease begins to **remit after about 2 days**, and the condition markedly improves within 4-5 days.

2- Any delay in treatment increases the likelihood of **complications** and recovery time.

Complications

1- Intestinal manifestations

- The 2 most common complications of typhoid fever include intestinal **hemorrhage** (12% in one British series) and **perforation** (3%-4.6% of hospitalized patients).
- **Perforation:**
  - Typically occurs in the 3rd week
  - Toxic patients may show few signs of peritonitis except for abdominal distension, increasing toxaemia and a rising pulse
  - Approximately 75% of patients have vomiting, severe abdominal pain, guarding, rebound tenderness and rigidity particularly in the right lower quadrant.
  - Diagnosis is difficult in the approximately 25% of patients with perforation and peritonitis who do not have the classic physical findings. In many cases, the discovery of free intra-abdominal fluid is the only sign of perforation.
  - The liver dullness is diminished and bowel sounds may be absent

- Blood count usually reveals leucocytosis
- X-ray of the abdomen usually shows collection of air under the diaphragm
- Surgery is preferable to conservative management
- Excision or segmental resection is safer than simple suturing because the gut wall immediately surrounding the perforation may be too friable to hold sutures
- Antibiotics should cover gram +ve, gram –ve and anaerobic organisms

- **Hemorrhage:**
  - Common in the 3rd and 4th weeks of illness
  - Patients may have repeated small bleeds that resolve without specific treatment
  - Or a single massive tarry bleeding which is typically a complication of the 3rd week
  - Pea soup like diarrhea is a good warning sign few days before the occurrence of bleeding and necessitates prompt treatment
  - Clinically the patient may have rapid thread pulse, hypotension and drop of temperature. Air hunger and cold sweats may occur in severe cases
  - Surgery is seldom needed provided that blood transfusion is available
  - Mechanism: may be erosion of blood vessel by the ulcers or due to coagulative defect or both

2- Neuropsychiatric manifestations

- **Severe toxaemia** → A toxic confusional state, characterized by disorientation, delirium, restlessness, stupor, obtundation or coma often accompanied by haemodynamic shock (not caused by GI hemorrhage) is characteristic of late-stage typhoid fever. In some cases, these and other neuropsychiatric features dominate the clinical picture at an early stage.
- Facial twitching or convulsions may be the presenting feature.
- Meningismus is not uncommon
- Frank meningitis is rare and usually occurs in young children .

- Encephalomyelitis may develop, and the underlying pathology may be that of demyelinating leukoencephalopathy. In rare cases, transverse myelitis, polyneuropathy, or cranial mononeuropathy develops.
- Focal intracranial infections are uncommon, but multiple brain abscesses have been reported.
- Other less-common manifestations: include spastic paraplegia, peripheral or cranial neuritis, Guillain-Barré syndrome, schizophrenia like illness, mania, and depression.

3- Respiratory

- Cough
- Ulceration of posterior pharynx
- Occasional presentation as acute lobar pneumonia (pneumotyphoid) in the 2nd or 3rd week (rusty sputum is not produced)

4- Cardiovascular

- Nonspecific ECG changes occur in 10%-15% of cases
- Toxic myocarditis :
    - Occurs in 1% - 5% esp. in toxic cases
    - A significant cause of death in endemic countries.
    - Characterized by tachycardia, weak pulse and heart sounds, hypotension, and ECG abnormalities.
    - Circulatory collapse may occur as early as the first day of the disease up to 50th day with an average of 15 days
- Pericarditis is rare, but peripheral vascular collapse without other cardiac findings is common.

5- Hepatobiliary

- Mild ↑ of ALT and AST: without symptoms is common
- Jaundice: may occur in typhoid fever and may be due to hepatitis, cholangitis, cholecystitis, or hemolysis.
- Pancreatitis and accompanying acute renal failure and hepatitis with hepatomegaly have been reported

6- Genitourinary manifestations

- Approximately 25% of patients with typhoid fever excrete *S typhi* in their urine at some point during their illness.
- Immune complex glomerulitis and proteinuria have been reported, and IgM, C3 antigen, and *S typhi* antigen can be demonstrated in the glomerular capillary wall.
- Nephritic syndrome may complicate chronic *S typhi* bacteremia associated with urinary schistosomiasis.
- Nephrotic syndrome may occur transiently in patients with glucose-6-phosphate dehydrogenase deficiency.
- Cystitis: Typhoid cystitis is very rare. Retention of urine in the typhoid state may facilitate infection with coliforms or other contaminants.
- Renal failure may occur and recovery after successful chemotherapy is usual

7- Hematologic manifestations

- Subclinical DIC is common in persons with typhoid fever.
- Hemolytic-uremic syndrome is rare.
- DVT may occur
- Hemolysis may be associated with G6PD ↓ (typhoid depresses G6PD levels in normal as well as in deficient patients)

8- Musculoskeletal and joint manifestations

- Skeletal muscle characteristically shows Zenker degeneration, particularly affecting the abdominal wall and thigh muscles.
- Clinically evident polymyositis may occur.
- Suppurative arthritis and is very rare and most often affects the hip, knee, or ankle (may be greatly delayed in onset)
- Osteomyelitis may occur (may be greatly delayed in onset)

9- **Late sequelae** (rare in untreated patients and exceedingly rare in treated patients)

- Neurologic - Polyneuritis, paranoid psychosis, or catatonia
- Cardiovascular - Thrombophlebitis of lower-extremity veins
- Genitourinary -Orchitis
- Musculoskeletal
  - Periostitis, often abscesses of the tibia and ribs
  - Spinal abscess (typhoid spine; very rare)
- Typhoid abscesses esp. in the spleen, liver, brain, breast
- Suppurative parotitis

10- **Chronic salmonellosis** → see later

11- **Typhoid relapse**

- Defined as return of symptoms and isolation of the original salmonella type from the blood at least 3 days after the patient initially becomes asymptomatic
- For a relapse to occur, a focus of infection must persist in the body (usually the gall bladder or necrotic foci in the mesenteric lymph nodes) after therapy
- The relapse usually occurs after an average apyrexial period of 15 days with a range from 5-80 days

12- **Typhoid carrier**

- It discharges bacilli for more than 12 months
- Foecal carriers are much more common in western countries than urinary carriers (ratio 10:1)
- This ratio is completely reversed in Egypt where chronic urinary excreters of salmonella typhi and paratyphi A reach about 3% of the population in rural areas
- These urinary carriers are usually associated with S. haematobium infection which causes damage to the urinary tract paving the way for chronic urinary tract infection with salmonellae

Investigations

Laboratory studies

1- **<u>The diagnosis of typhoid fever is primarily clinical</u>** [gradual onset, remittent fever, toxic look, bronchitic chest, tumid tympanitic abdomen and soft tender spleen are suggestive criteria of the disease]

2- **<u>Blood culture</u>**

- The method of choice for diagnosis of typhoid fever
- The organism is found in the blood during the first week and disappears shortly after antibiotic treatment
- Positive for *S typhi* in approximately 85%-90% of patients who present within the first week of onset
- Blood is cultured in a selective medium (e.g., 10% aqueous oxgall) or a nutritious medium (e.g., tryptic soy broth) and are incubated at 37°C for at least 7 days. Subcultures are made daily to one selective medium (eg, MacConkey agar) and one inhibitory medium (eg, *Salmonella-Shigella* agar). Identification of the organism usually takes 48-72 hours
- Multiple blood cultures (>3), large-volume (10-30 mL) blood culture and clot culture may increase the likelihood of detection.
- Multiple blood cultures (>3), large-volume (10-30 mL) blood culture and clot culture may increase the likelihood of detection.

3- **<u>Stool culture</u>**

- The organism is found in the stool throughout the course of illness but most readily isolated during the 2nd and 3rd week
- Sensitivity < 50% and does not confirm the diagnosis as the patient may be a chronic carrier
- Accu –chek S. typhi test for direct detection of antigens in stools is a rapid, sensitive and specific test

4- **<u>Urine culture:</u>** less sensitive. The organism found in urine from the 2nd week onwards (intermittent), used for detection of carriers

5- **Bone marrow culture** → give higher positive rates as the conc. of organisms is 10-fold higher than in blood and +ve results may yield after chemotherapy has started [not done in practice as the string capsule for duodenal aspirate]

6- **Aspirates from** rose spots, CSF or pus from abscess may give positive cultures

7- **PCR:** Nested PCR has achieved a sensitivity of 82.7% and specificity of 100%. But not widely available

8- **Widal agglutination test:**

- It is used to measure agglutinating antibodies against H and O antigens of S typhi.
- Neither sensitive nor specific, the Widal test is no longer an acceptable clinical method. It is a suggestive rather than a diagnostic test
- However, if the test is interpreted intelligently, a significant number of patients will be correctly diagnosed by the widal test when all other methods have failed
- Antibodies to salmonella appear in the serum during the 2nd week and reach maximum titre during the 4th week
- Interpretation of widal test: for proper interpretation, 2 serum samples separated by 10 days interval should be tested. The detection of a rising titre in the 2nd serum sample indicates active enteric fever. However, if only one sample is available, the following facts should be taken into consideration:

  - High titre of O and H (≥ 1/160) or rising titre → indicates recent active infection. Note that O antibodies disappear faster than H antibodies
  - High titres of H only ((≥ 1/160) → suggest past vaccination or past infection
  - If the test is done during the 1st week, it gives false –ve results as antibodies start to appear during the 2nd week and onward
  - In Egypt, titres < 1/80 are of no significance due to endemicity of the disease and previous subclinical infection
  - Early antibiotic treatment lowers the antibody titre due to reduction of the antigenic mass

- Non enteric infections by other salmonella or autoimmune diseases may cause a non specific rise of antibody titre, due to the presence of cross reacting antibodies
- High titres to Vi antigen (if included in the test) occur in some carriers

9- Other serological tests:

- Indirect hemagglutination, indirect fluorescent Vi antibody, and indirect ELISA for IgM and IgG antibodies to S typhi polysaccharide, as well as monoclonal antibodies against S typhi flagellin, are promising, but with variable success rates

10- Other nonspecific laboratory studies

- CBC
  - Most patients are moderately anemic, have thrombocytopenia, and relative lymphocytosis.
  - TLC normal or ↑, leucopenia rare at the present time (early multiple antibiotics)
  - Eosinopenia is suggestive of the disease
- PT, PTT: slightly ↑ in most patients with decreased fibrinogen levels.
- Circulating fibrin degradation products: commonly ↑ to levels seen in subclinical DIC
- ALT, AST and serum bilirubin values: usually ↑ to twice the reference range. And returning to normal on recovery
- Indirect bilirubin → often associated with haemolytic anemia in patients with G6PD ↓ and in children
- Albuminuria → in severe cases
- Mild hyponatremia and hypokalemia are common.
- A serum ALT–to–LDH ratio of > 9:1 appears to be helpful in distinguishing typhoid from viral hepatitis: A ratio of > 9:1 supports a diagnosis of acute viral hepatitis, while ratio of < 9:1 supports typhoid hepatitis.

Imaging studies

1- **X-ray of the abdomen** → usually show air under the diaphragm if perforation occurred

2- **Radiography**: Radiography of the kidneys, ureters, and bladder (KUB) is useful if bowel perforation (symptomatic or asymptomatic) is suspected.

3- **CT scanning and MRI:** if abscesses in the liver or bones, among other sites are suspected

Staging

1- **Uncomplicated typhoid fever**

2- **Complicated typhoid fever** (in up to 10% of treated patients) is characterized by:

- Melena (3% of all hospitalized patients with typhoid fever)
- Serious abdominal discomfort
- Intestinal perforation
- Marked neuropsychiatric symptoms, or other severe manifestations.

Treatment

1- **Supportive measures**

- Bed rest
- Non-roughage diet
- Adequate fluid and electrolyte replacement

2- **Outpatient or admission?**

- Many patients in endemic areas are effectively managed as outpatients
- Severely ill patients who may be mentally uncooperative require admission

3- **Specific chemotherapy**

- The drug of choice is → chloramphenicol
- Alternatives → amoxicillin or co-trimoxazole
- MDR isolates of S. typhi and S. paratyphi A to all 3 antibiotics have been widely reported
- Treatment of MDR infections

- Fluoroquinolones
- 3rd generation cephalosporins
- Azithromycin

- Widespread use of fluoroquinolones has led to the emergence of strains with low level and full resistance to these antibiotics
- Relapses after chemotherapy
  - Occur in 2-10%
  - Less severe and respond to the same chemotherapy

4- Chloramphenicol

- Effect
  - Commonly takes 48 h before the fever subsides
  - In severe cases → 5 days or more until the patient becomes completely afebrile
- Side effects and monitoring
  - Bone marrow depression → serial weekly TLC required
  - Hexheimer type reaction , sometimes seen early in treatment → steroids required
- Duration of treatment → 12 days after the fever has abated to prevent relapse

5- Amoxicillin

- As effective as chloramphenicol if given in high doses
- Ampicillin is inferior to chloramphenicol

6- Co-trimoxazole

- The clinical response is at least as rapid as chloramphenicol

7- Fluoroquinolones

- Effect → a 5-7 day course has proved extremely effective for the treatment of fully susceptible isolates with rapid resolution of fever and symptoms

- Use in children → previously not recommended before 14 yr (damage to cartilage in the growing joints of animals), but now approved to be used safely in children
- Diagnosis of resistance
    - Clinical → the patient still sick and febrile after 5-7 days of an adequate dose
    - Laboratory → difficult, but resistance to the related antibiotic nalidixic acid is a useful marker
- Treatment of resistant infections
    - Gatifloxacin
    - Ceftriaxone

8- 3rd generation cephalosporins

- Effective in MDR infections, but the response frequently slow with the fever and symptoms taking 7-10 days to resolve

9- Steroids

- Indications → limited to severe toxic cases
    - Delirium or Obtundation
    - Shock or coma
- Dose → dexamethasone 3mg/kg by slow I.V. infusion over a period of 30 min followed by 1mg/kg given at the same rate every 6 h for 8 additional doses [hydrocortisone given at a lower dose not effective]

10- Treatment of chronic carriers

- Ciprofloxacin 750mg twice daily for 28 days is effective **or**
- 2 tablets of co-trimoxazole twice daily for 3 months **or**
- Amoxicillin 100mg/kg/day + probenecid 30 mg/kg/day for 3 months
- Faecal carriers respond temporarily to chemotherapy, but Cholecystectomy needed to terminate the carrier state

Antibiotic	Dosage	Freq.	Route	Non-severe	Severe or complicated	Side effects
Chloramphenicol	50-100 mg/kg/day ; reduce dose to 30mg/kg/day when fever ceases	4	O(i.m/i.v)	14-21 day	14-21 day	Bone marrow depression
Amoxicillin	75-100mg/kg/d	3	O(i.m/i.v)	14	14	
Co-trimoxazole	8+40 mg/kg/day	2-3	O(i.m/i.v)	14	14	Nephrotoxic Allergy Not for children< 2 yrs
Ciprofloxacin[a]	20mg/kg/day	2	O (i.v.)	5-7	10-14	
Ofloxacin[a]	15mg/kg/day	2	O (i.v.)	5-7	10-14	
Gatifloxacin[a]	10mg/kg/day	1	O (i.v.)	5-7	10-14	
Ceftriaxone	50-80mg/kg/day	1-2	i.m./i.v.	7-10	10-14	
Cefotaxime	100-150mg/kg/d	3-4	i.m./i.v.	7-10	10-14	
Cefixime	20-30mg/kg/day	2	O	7-10	Not recommended	
Azithromycin	20mg/kg/day	1	O	5-7	Not recommended	

[a]Nalidixic acid resistant isolates may not respond

Typhoid vaccine

1- **Recommended in** highly endemic areas with high rates of antimicropial chemotherapy

2- **Live attenuated oral vaccine (Ty21a)**

- 3 oral doses over 5 days
- Booster recommended every 5 years
- Not recommended < 6 yrs

3- **Purified Vi antigen vaccine**

- Single I.M. dose
- Boosters recommended every 3 years
- Not recommended < 2 yrs

Chronic salmonellosis

Definition

1- Characterized by **prolonged fever and bacteremia** in **bilharzial** patients

2- It is suggested that salmonellae can penetrate the schistosomes, multiply within their ceca, thus schistosomes act as a nidus producing showers of salmonellae into the circulation

Complicating S. haematobium

Clinical features

1- Usually **remittent or intermittent type of fever** of long duration (1-24 months) with frequent chills

2- **Dysuria and terminal hematuria** are common

3- Toxicity is not characteristic of the disease

4- HSM is not uncommon

5- No significant tympanitis or tenderness of the abdomen is elicited

6- The condition mimic the clinical picture of urinary tract infection

Investigations

1- Repeated blood & urine cultures

- During the fever spike usually reveals S. paratyphi A 5 times more than S. typhi

2- CBC → usually within normal WBCs

3- Widal test → usually shows low or moderately elevated titres

4- Urine examination

- Usually reveals S.haematobium ova, pyuria, RBCs and a variable amount of albumin

5- IV pyelography

- Usually shows damaged urinary tract and evidence of obstructive uropathy

- Bilharzial patients usually have damaged urinary tract in which the salmonella reside and from which they are shed intravascularly intermittently

Complicating S. mansoni

Clinical features

1- Usually **continuous or remittent type of fever** of long duration (1-24 months) with frequent attacks of chills and diarrhea

2- Anorexia, epistaxis, loss of weight and abdominal pain are common

3- The patient looks toxic and pale

4- Generalized **lymphadenopathy** is common

5- **Jaundice, edema of the lower limbs**, petechial rash and purpuric eruptions are usually elicited

6- Significant **HSM** is a constant feature

7- Ascites is rare

8- The condition mimic the clinical picture of **kala-azar**

Investigations

1- **Repeated blood cultures**

- During the fever spike usually reveal S. typhi 4 times more than S. paratyphi A

2- **CBC**

- Usually within normal WBCs or leucocytosis
- Anemia, thrombocytopenia and ↑ ESR are constant findings

3- **Widal test** → usually shows low or moderately elevated titres

4- **Stool examination**

- Usually reveals S. mansoni ova
- Rectal snip examination by transparency technique usually shows S. mansoni ova when stool examination is negative

5- Hypergammaglobulinaemia and abnormal liver function tests → are common findings

Treatment

1- Eradication of the salmonellae from the circulation → by **antityphoid drugs**

2- Prevention of relapses → by **antischistosomal drugs**

- Chloramphenicol or co-trimoxazole for 10 days +
- Praziquantel 40 mg/kg as a single oral dose given on the 2nd a pyrexial day under chloramphenicol therapy

Paratyphoid A and B

1- Infection usually via contaminated **food**

2- Diarrhea and vomiting may precede septicaemia

3- Manifestations as typhoid fever, but many **mild cases** occur

4- Treatment and drug resistance the same as typhoid fever

Paratyphoid C

1- Commonly produce **septicaemia** without gut involvement

2- Abscess formation is common

Tularaemia

Etiology and pathogenesis

1- **Causative organism → <u>Francisella tularensis</u>**

- <u>The organism</u>
  - Poorly staining, tiny Gram-negative coccobacilli.
  - Organisms are strict aerobes that grow best on blood-glucose-cysteine agar at 37°C
  - Facultative, intracellular bacterium that multiplies within macrophages
- <u>Major target organs:</u>
  - Lymph nodes, lungs, pleura, spleen, liver, and kidney
- <u>Infectivity and pathogenicity</u>
  - One of the most infectious pathogenic bacteria known
  - Inoculation or inhalation of as few as ten organisms can cause disease.
  - Extreme infectivity
  - Substantial capacity to cause illness and death
  - Can survive for weeks in Water, Soil, Moist hay, Straw, Decaying animal carcasses because it is…Hardy, non-spore forming organism

2- **<u>Reservoirs:</u>** Small and medium sized mammals are the principal natural reservoirs for *F. tularensis* (zoonosis):

- <u>Rabbits</u> الأرانب
- Aquatic <u>Rodents</u> (Beavers, Muskrats) القوارض المائية- القنادس وفئران المسك
- <u>Rats</u> الجرذان
- <u>Squirrels</u> السناجب
- <u>Lemmings</u> القوارض
- <u>Mice</u> الفئران
- <u>Birds and deer</u> الطيور والغزلان

3- **Vectors** →Hard Ticks (Ixodes and demenecator), Mosquitoes, Biting Flies

4- **Also Known As:**

- Deer-fly fever (Utah)
- Glandular tick fever (Idaho and Montana)
- Market men's disease (Washington D.C.)
- Rabbit fever (Central States)
- O'Hara's disease (Japan)

5- **Transmission:**

- Handling of infected animals during skinning or cooking
- Bite of infected blood-sucking deer flies and wood ticks (50% of cases attributed to the bite of ticks)
- Ingestion of improperly cooked meat or contaminated water.
- Aerosol inhalation from contaminated environment contaminated by rodent excreta
- Contamination of conjunctival membrane
- No human to human transmission

6- **Type A –tularensis:**

- Most common biovar isolated in North America
- May be highly virulent in humans and animals
    - Infectious dose of < 10 CFU
    - Mortality of 5-6% in untreated cutaneous disease

7- **Type B—palaeartica (holartica):**

- Thought to cause all of human tularemia in Europe and Asia
- Relatively a virulent
    - Mortality < 5% in untreated cutaneous disease

Clinical features

1- Incubation period --- 1-21 days *average = 3-5days), clinical presentation depend on the route of inoculation

2- Duration of illness --- ~2 weeks

3- Mortality --- treated: low **&** untreated: moderate

4- General manifestations

- Fever, chills and low back pain
- Temperature pulse dissociation is a classic finding
- Multiple symptom complexes may occur simultaneously

5- Ulceroglandular → 80% of cases

- Peripheral focus→pustule→ulcer 1-14 days after bite (ulcers are necrotic, painful and erythematous)
- In rabbit associated disease → the ulcer located in on a finger or hand in > 90% of patients
- In tick borne disease → the ulcer found on lower extremity or perineal area in 50%, the trunk in 30% and the head in 5-10%
- Regional lymphadenopathy which may suppurate
- Systemic manifestation: Fever, chills and myalgia

6- Glandular

- Similar to ulceroglandular type (tender localized lymphadenopathy) except for the absence of the characteristic skin lesion

7- Oropharyngeal (throat) and gastrointestinal:

- Sore throat
- Mild pseudomembranous pharyngitis (rare)
- Cervical and retropharyngeal lymphadenopathy
- Mesenteric lymphadenopathy
- Diarrhea (persistent, fulminant and can be fatal)

8- Oculoglandular (eye):

- Painful purulent conjunctivitis
- Regional lymphadenitis (preauricular, submandibular or cervical)
- Vision loss is rare

9- Typhoidal (septicaemic):

- Severev febrile illness
- Chills, headache, myalgias, sore throat, anorexia, vomiting, diarrhea, abdominal pain and cough

- Abscent lymphadenopathy and skin lesions
- Pneumonia is common
- Most difficult to diagnose
- Severe cases may progress to hyponatremia, rhabdomyolysis, renal failure and sepsis

10- <u>Pneumonic:</u>

- Cough, pleuritic pain, focal patchy or lobar infilteration
- Mediastinal and hilar lymph nodes
- 2ry to inhalation or hematologic spread of the above forms esp. ulceroglandular or typhoidal

Diagnosis

1- Clinical.

2- Culture: **glucose cysteine agar.**

- Rarely seen on gram stain
- Culture is difficult and dangerous (the organism can be transmitted by aerosol from actively growing cultures)

3- Serodiagnosis:

- Agglutination with titre >1:160 or a 4 fold rising titre (Response from antibody does not occur until several days after onset of disease)
- ELISA

Treatment

1- <u>Streptomycin and aminoglycoside (gentamicin) :</u>

- <u>Dose</u>
  - Streptomycin → 1 gm I.M for 10 days or (15 mg/kg i.m. q12) [drug of choice]
  - Gentamicin → 5 mg/kg/day i.v. for 10 days is nearly effective
- <u>Pros</u>
  - Effective against tularemia
- <u>Cons</u>
  - Require intramuscular or intravenous administration

- High toxicity profile
- Can be relapses of tularemia on aminoglycosides
- There exist streptomycin-resistant strains of *F. tularensis*

2- Tetracycline and chloramphenicol:

- Dose
  - Tetracycline → 500 mg/ 6 hrs for 2-3 weeks
  - Doxycycline → 100 mg/12 hr for 2-3 weeks
  - Chloramphenicol → 500 mg/ 6 hrs
- Pros
  - Effective against tularemia
  - Can be administered orally
  - Low toxicity
- Cons
  - Higher relapse rate than aminoglycosides

3- Quinolines (including ciprofloxacin):

- Dose → 200 mg twice daily
- Pros
  - Generally works well
  - Low relapse rate
  - Can be administered orally
- Cons
  - Has not been used extensively for treatment

4- Tularemia meningitis

- Aminoglycoside plus i.v. chloramphenicol

5- Vaccine: Live attenuated administered by multiple punctures for high risk groups

Bartonellosis (including cat scratch disease)

Pathogenesis

1- Causative organism (intracellular gram –ve bacilli**)**

- Bartonella henselae is statistically linked to cat exposure.
- Bartonella quintana is associated significantly with body louse infestation and homelessness (humans are the 1ry reservoir).

2- Diseases

- Both B. henselae and B. quintana cause
  - Cat scratch disease (esp. in children)
  - Bacillary angiomatosis (in HIV)
  - Trench fever
  - Relapsing bacteremia
  - Endocarditis
- Only B. henselae can cause → bacillary peliosis hepatis (in HIV)
- Only B. henselae and B. quintana infections have been identified in HIV-infected persons
- Bacillary angiomatosis most often occurs late in HIV infection, in patients with a median CD4+ count of <50 cells/μL

3- Distribution and prevalence

- Worldwide distribution
- Prevalence in warm/humid climates
- ~ 20,000 cases annually in US
- 80% under the age of 20yrs
- 30% of domestic cats are infected

4- Mode of infection

- By scratches (esp. by kittens) and bites, as well as bites from lice, fleas and ticks

Clinical features

1- **Bacillary angiomatosis**

- Lesions have been associated with nearly every organ system (visceral, neurologic and bone involvement can be seen) but cutaneous most common
- Lesions can be clinically indistinguishable from Kaposi Sarcoma (dark violaceous subcutaneous vascular nodules which may be numerous)
- Osteomyelitis is usually caused by *B. Quintana*
- Hematogenously disseminated infection, and systemic symptoms of fever, night sweats, and weight loss *(CD4<100)*

2- **Peliosis hepatis**

- It is a visceral manifestation of disseminated bartonellosis
- Presents as vomiting, diarrhea, HSM and fever

3- **Urban trench fever**

- Characterized by fever, headache, body pain and conjunctival injection
- Can be a single self limited episode or classically, a chronic debilitating relapsing illness with episodes that last around 5 days each

4- **Cat scratch disease** → ® see below

Diagnosis

1- **Bacilliary Angiomatosis & Peliosis**

- Bacteria detectable in lesions (modified silver stain e.g. Warthin-Starry stain)
- Tissue biopsy → characteristic pattern of blood vessel proliferation
- Serology
- PCR
- IFA
- Blood culture (EDTA tubes) for BacilliaryAngiomatosis [culture not useful in diagnosis of CSD]

2- **Cat scratch disease** → see below

Cat scratch disease

Definition

1- Cat scratch disease is characterized by tender regional chronic **lymphadenopathy** preceded by primary skin lesion related to cat scratch.

2- The disease is usually benign and the adenopathy **resolves spontaneously** in 3 weeks to several months.

Etiology

1- **Causative organism** → Bartonella henselae a pleomorphic gram-negative bacilli.

2- **Vector** → Ctenocephalidesfelis vector

Clinical features

1- Incubation period → Usually 3-10 days elapse from the time of scratch or contact with a cat

2- **Primary skin papule or pustule**

3- Then a **vesicular lesion** appears :

- Which oozing fluid which dries forming a scar.
- The most frequent affected parts are the upper extremities followed by the cervical and facial regions.

4- About 3 weeks after the primary lesion, painful **regional lymphadenopathy** becomes manifest:

- Lymphadenopathy is usually unilateral and involves most commonly the axillary, epitrochlear, cervical or inguinal lymph nodes.
- Lymphadenopathy persists for 2-4 months.

5- **Fever** lasts for 5-21 days with malaise (common causes of FUO in children)

6- **Splenomegaly** may occur in 25% of cases (may be HSM)

7- **Oculoglandular syndrome** in the form of conjunctivitis, Salivary gland enlargement and lymphadenopathy occur in 20%.

8- **Rare clinical findings** include

- CNS involvement

- Severe chronic systemic disease
- Osteomyelitis.
- Culture negative endocarditis and bacteremia

9- Endocarditis and bacteremia

- May be associated with conjunctival injection, maculopapular rash, lymphadenopathy or HSM
- Leukocytosis and thrombocytopenia may be present
- Native valves are most commonly affected

10- Neurological deficits (uncommon)

- Encephalopathy: headache, mental status changes, seizure, hemiplegia and ataxia
- Retinal neuritis and transverse myelitis

Diagnosis should fulfill 3 of the following 4 criteria:

1- History of cat scratch contact with presence of primary dermal lesion.

2- Negative laboratory studies for other causes of lymphadenopathy ®

3- Lymph node biopsy revealing typical histology:

- Demonsteration of stellate (necrosis) shaped granulomas consisting of accumulation of polymorphnuclear leucocytes and fibrin deposits surrounded by palisading epitheloid cells.
- The central area of the nodes is surrounded by microabscesses which tend to break into fibrofatty tissues.
- Cat scratch bacilli are best demonstrated by the ***Warthin-Starry silver stain.***

4- A positive skin test using cat antigen (serology):

- Positive in 98% of patients who are suspected of cat scratch disease.
- Positive IgM (≥ 1:160) or high IgG titre (> 1:256) suggests current bartonella infection
- Decrease in antibody titre should follow 10-14 days after antibiotic treatment
- An IgG titre of > 1:800 suggests chronic infection

- Cross reactivity occurs between bartonella, Chlamydia and coxiella spp. → this can lead to confusion between inguinal cat scratch and lymphogranuloma venereum foe example

- **N.B. [PCR of tissue]:**
  © Very sensitive and specific
  ©It is of particular use on heart valve tissue to diagnose culture negative endocarditis caused by bartonella as it is not affected by prior use of antibiotics

Treatment

1- CSD: Appropriate **follow up and conservative** symptomatic treatment

- The disease is self-limited; however, symptoms may last several weeks

2- Analgesics and antipyretics if needed

3- Local heat may be applied to the involved lymph nodes

4- Aspiration if suppuration occurs

5- **The efficacy of antimicrobial therapy is unproven :**

- Antibiotics are not indicated in most cases of CSD
- Indicated in
  - Severe or systemic disease.
  - Severe, painful lymphadenopathy; however, no reduction in the duration of symptoms has been shown.
  - Immunocompromised patients they are particularly susceptible to systemic disease and bacteremia
- Severe disease was defined as:
  - Persistent high fever [>39.5˚C]
  - With severe systemic signs (eg, malaise, fatigue, blindness, headache) and lymphadenitis
- Drugs used :
  - Drug of choice → azithromycin 500 mg PO daily on day 1 followed by 4 days of 250 mg PO daily

- Alternatives → erythromycin, doxycycline, rifampin, ciprofloxacin, gentamicin intramuscularly, trimethoprim/sulfamethoxazole (TMP-SMZ)

- Antibiotic resistance
  - Penicillin
  - Amoxicillin
- These agents were considered moderately to highly effective, producing reduction or resolution of lymphadenopathy, a declining erythrocyte sedimentation rate, and decreased inflammatory and constitutional symptoms within 3-10 days

6- Special considerations:

- Disseminated CSD or trench fever → requires at least 4 weeks of therapy
- Peliosis hepatis and bacillary angiomatosis → requires 3-4 months of therapy
- Retinitis → treated for 4-6 weeks with a combination of rifampicin and doxycycline or azithromycin
- Endocarditis → treated with ceftriaxone and gentamycin and/or doxycycline for 6 weeks. Valve replacement is often required

7- The efficacy of steroid therapy is controversial

- Patients with atypical CSD [neuroretinitis, encephalopathy with or without hemiplegia, and acute solid organ transplant rejection] should treated by a combination of appropriate antibiotics and steroid therapy

8- Suppression (bacillary angiomatosis and peliosis)

- Long-term suppression of infection with doxycycline or a macrolide is recommended, as long as the CD4+ count remains <200 cells/μL.
- Discontinued after the patient has received 3–4 months of therapy and when the CD4+ count remains >200 cells/μL for ≥6 months.

Prevention

1- Persons who acquire a cat should acquire an animal aged >1 year and in good health.

2- Homeless or marginally housed individuals should be educated that body louse infestation can be associated with serious illness.

Melioidosis (Pseudoglanders or Whitmore disease)

Pathogenesis

1- **<u>Causative organism</u>** → Burkholderia pseudomallei

- Previously called <u>Pseudomonas pseudomallei</u>
- "Melioidosis" is derived from the Greek word meaning glanders-like illness or distemper of the asses
- It is an aerobic, gram-negative motile bacillus found in water and moist soil and is endemic in tropical and subtropical countries.
- It is an opportunistic pathogen that produces exotoxins.
- Because it can survive in phagocytic cells, latent infections are a common disease manifestation.

2- **<u>Contact of skin wounds with contaminated soil or water</u>** → The most common way

- Contact of skin wounds with contaminated soil or water → The most common way
- Aspiration or ingestion of contaminated water
- Inhalation of dust from soil
- Transmission between infected animals and/or infected people is very rare
- Person-to-person transmission has been described rarely, generally to family members in close contact (e.g. family members who nursed patients).
- Sexual transmission has also been suggested in some cases.

- Vertical transmission has rarely been proven, although a few cases were described in newborns.
- One infant may have contracted the bacteria by nursing culture-positive breast milk.

3- <u>Distribution</u>

- Meliodosis occurs in several areas in the tropics and subtropics. Most endemic regions are between the latitudes of 20 ^{o}N and 20 ^{o}S.
- Melioidosis is endemic in: **Southeast Asia, China, the Indian subcontinent and parts of Australia.**
- It has also been reported from: **The Caribbean, the Middle East, South America, Singapore and Taiwan.**
- The situation in Africa is uncertain. Although isolated cases were reported from some African countries in the past, melioidosis is not a commonly reported disease in Africa. In the U.S., isolated cases have also been reported in Hawaii and Georgia; however, most were associated with travel abroad.
- Clinical disease is relatively uncommon. In certain endemic areas, 5 to 20% of agricultural workers have antibodies to B. pseudomallei; however, they have not shown overt disease. Outbreaks and cases typically occur during the wet season or after periods of heavy rainfall in areas with high humidity or temperature.

4- <u>Melioidosis is listed by the CDC as a Category B potential bioterrorism agent</u>

- This indicates agents which are moderately easy to disseminate. Additionally, moderate morbidity and low mortality is noted with these agents. Specific diagnostics will be required in the event of an attack. As an agent, Burkholderia pseudomallei can be very stable in the environment, persisting for months. However, it can be killed very easily by heat.

Clinical features

1- **Incubation period**

- Variable incubation period from less than 1 day (after very high exposure) to several months to many years.
- Due to the ability of B. pseudomallei to survive in phagocytic cells, many cases of melioidosis occur after a latent period.
- Immunosuppressive events or chronic diseases, such as diabetes mellitus or renal disease, have been reported to be a risk factor for disease reoccurrence.

2- Most infections are: **asymptomatic**

- When clinical disease develops, many manifestations can occur

3- **Acute pulmonary infection** → The most common form

- Infection may occur either through inhalation or by septicemic spread of the organism to the lungs.
- It is demonstrated by a high fever, headache and pneumonia with caseous lesions. A dull aching chest pain, cough, tachypnea, and rales can also occur.
- Chest x-rays may show upper lobe consolidation, nodular lesions or pleural effusion.

4- **Focal melioidosis:**

- Additionally, melioidosis can be limited to a focal infection. Localized lesions may occur in the skin (as a result of infected wounds) or various internal organs (as a result of septicemic spread). Many times focal infections become chronic conditions.
- Involves abscess formation in various tissues or organs. The lesions can be either acute (abscess) or chronic (granulomatous). Infection typically occurs from a contaminated wound or trauma. Skin, bone, muscle and joints may be affected this way. Hematogenous spread from wounds may then further infect internal organs such as the liver, spleen, heart,

and genitourinary tract. Infrequently infection of the nervous system may occur, resulting in meningitis, encephalitis and motor paralysis.

5- **Septicemic melioidosis:**

- The disease can also occur in a severe septicemic form. This can either be non disseminated (only involving one organ) or disseminated.
- Is acute in onset and fatal without treatment. Clinical signs for this form of melioidosis include high fever, tachypnea and dyspnea, myalgia, hepatosplenomegaly, and septic shock. Additionally, disorientation, severe headache, pharyngitis, diarrhea and pustular skin lesions may be noted. This form of melioidosis is rapidly progressive with a mortality of 90% without treatment and 50% with treatment. It has been reported that the onset of septicemic or chronic melioidosis is much more common in persons suffering from a debilitating illness, such as diabetes mellitus.

6- **Neurological disease**

- Finally, on rare occasions

Diagnosis

1- **Diagnosis of melioidosis is difficult:**

- It has been called the great imitator because there are no pathognomonic lesions.
- Isolation of the organism from blood, sputum, tissues or wound exudates can help to diagnose the disease.
- Serological tests for titers may also be used for diagnosis. Serological tests available include agglutination tests, indirect hemagglutination, complement fixation, immunofluorescence and enzyme assays.
- Cross-reactions may occur in serologic tests with Burkholderia mallei (causative agent for glanders).

2- **Clinical:**

- Endemic area.
- Immunosuppression.

- Septicemia.
- Multiple abscesses.
- Demonstration of bipolar gram negative bacilli in films of pus or secretions
    - Stain: Wayson and Wright.
    - Culture: on methylene blue agar or Mcconkey.

Treatment

1- B. Pseudomallei is variably susceptible to antibiotics.

2- **Long-term treatment** and multiple drugs will be necessary for chronic and severe cases.

3- **Relapses**, as soon as 6 months after treatment, are common.

4- **Surgical drainage** of skin wounds can be effective for localized infection.

5- Currently there is **no vaccine available**, however, experimental vaccines used in dolphins and other cetaceans reduced mortality.

6- **Drugs**

- Ceftazidime or carbopenem parenteral for minimum 10 days.
- Sometimes Co-trimoxazole combined with Ceftazidime.
- Maintance dose of oral treatment to prevent relapse (Co-trimoxazole + Doxycycline) after parenteral treatment.

Prevention and control

1- Melioidosis is usually acquired from the environment, particularly after contact with soil or water. To minimize contact with dirt:

2- **Animals** can be raised on wooden slats, concrete or paved floors.

3- Providing safe drinking **water** is important in endemic areas.

4- B. Pseudomallei is particularly common in muddy water, and it is less likely to be found in fresh or clear water. Although small numbers of bacteria may survive treatment, **chlorination** of the water supply decreases the risk of infection.

5- Care should also be taken during **animal necropsies**. This is especially important for immunocompromised persons or anyone with a chronic medical condition such as diabetes mellitus or renal disease.

6- If **wounds** do become contaminated with soil or water, thorough cleaning of the wound with disinfectant soap and water will help to prevent infection.

Glanders

1- Disease of horses. In Middle East, Asia and Africa.

2- Causative Organism:

- Burkholderia mallei (previously called **Pseudomonas mallei**).

Contact with infected animals. Inhalations of dust contact with horse excreta.

3- Clinical features:

- Very close to melioidosis

4- Diagnosis:

- Culture on blood agar
- Films from pus stained with **Wayson and Wright**

5- Treatment:

- Co-trimexazole
- Tetracycline
- Aminoglycosides (streptomycin)

Anthrax

Etiology

1- It is primarly a disease of farm animals e.g. cattle and sheep and can transmitted to man

2- Organism:

- Bacillus anthracis
- Gram positive aerobic spore forming organism

3- Mode of transmission

- Contact with diseased animals or their dead bodies [butchering-the organism enters through skin abrasions- and eating infected meats] → cutaneous and GI disease

- Inhalation of spores [people handling wool from infected animals] → pulmonary type

Clinical types

1- **Cutaneous anthrax** (malignant pustule)
   - A papule forms which rapidly changes to a vesicle then a pastule and a necrotic ulcer covered by a painless black eschar and surrounded by marked edema
   - Infection may spread leading to septicemia

2- **Pulmonary anthrax** (Wool sorter's disease)
   - Presents initially with influenza like illness, GI symptoms or both
   - Followed by fulminant respiratory distress (hemorrhagic mediastinitis and bloody pleural effusion), septic shock, multiorgan failure and death

3- **Intestinal anthrax**
   - Vomiting, abdominal pain and bloody diarrhea
   - It is rarely reported

Use in bioterrorism

1- It is **a major agent** in biological warfare and bioterrorism

2- In 2001, an **outbreak** of 22 cases: 11 inhalation and 11 cutaneous anthrax occurred in the USA

3- The outbreak was caused by sending spores of the organism **through the mail**. 5 of the patients with inhalation anthrax died

Diagnosis

1- Clinical signs and history of exposure

2- **Inhalation type**
   - Suggested by a widened mediastinum without infiltrates on chest X-ray
   - Confirmed by blood culture [blood smears stained by MacFadyean stain may reveal the capsulated rods]

3- **Cutaneous and GI types**
   - Diagnosed by culture of blood or tissues (skin lesions)

4- **In case of a bioterror attack**

- Rapid diagnosis can be performed in special laboratories using PCR-based assays

Treatment

1- **Treatment with immediate antibiotic** initiation on first suspicion of inhalational anthrax reduces mortality

2- **Empiric therapy should be either**
   - Ciprofloxacin 400 mg IV bid **or**
   - Doxycycline 100 mg IV q12 **plus**
   - Two other antibiotics that are active against B. anthracis e.g. penicillin, clindamycin and vancomycin

3- **Duration of therapy**
   - Oral therapy with ciprofloxacin 500 mg PO bid or doxycycline 100 mg PO bid and one other active agent should be started after improvement and continued for 60 days to reduce the risk of delayed spore germination

4- **Uncomplicated cutaneous anthrax**
   - Can be treated with oral ciprofloxacin 500 mg bid or doxycycline 100 mg bid for the same duration

5- **Postexposure prophylaxis**
   - Oral ciprofloxacin 500 mg q12 for 60 days after exposure
   - Doxycycline or amoxicillin is an alternative if the strain proves susceptible

6- **Anthrax vaccine adsorbed**
   - Available in USA for human use (those with high occupational risk)

Prognosis

1- **The inhalational and intestinal anthrax** are often fatal as they go unrecognized early

2- Case fatality rate for inhalational type is **45%**

Toxic shock syndrome

Definition

1- It is a bacterial toxin mediated illness characterized by acute onset of fever, hypotension and multiorgan failure

Classification

1- Staphylococcal TSS

- Menstrual
- Non-menstrual

2- Streptococcal TSS

Etiology

1- Staphylococcal TSS

- Majority of cases by methicillin sensitive strains of S. aureus
- Several case reports by MRSA
    - [TSS toxin 1 & Staphylococcal enterotoxin B]

2- Streptococcal TSS → by S. pyogens

- Streptococcal pyrogenic exotoxins (SpeA, SpeB)

3- Bacterial superantigen (crucial component of the pathogenesis) trigger excessive unregulated T- cell activation which result in exaggerated systemic inflammatory response → that cause shock and multiorgan failure

Risk factors

1- High absorbency **tampons** for menstrual staphylococcal TSS

2- Disruption of skin or mm (abscess, surgical procedure, burns) in patients colonized or infected with the toxin-producing strains of S. aureus

3- Trauma, surgery, older age , chronic illness, varicella infection and NSAID use predispose patients to invasive streptococcal disease

4- 50% of the patients with **NF** will have associated TSS

5- 90% of staphylococcal TSS cases occur in **women** with roughly 50% of these being associated with menstruation [the incidence ↓ when most super-absorbancy tampons were removed from the market]

6- 15% of **invasive streptococcal diseases** cases (as cellulitis, NF or pyomyositis) will develop streptococcal TSS

Clinical features

1- Symptoms

- May present with an acute influenza like illness that rapidly progresses to shock and multiorgan failure within 8-12 hours after symptom onset
- History of menstruation with tampon use suggests staphylococcal TSS
- Patients may report a history of trauma or severe pain at the site of infection that can mimic peritonitis or MI

2- Signs

- Shortly after initial presentation the following may appear
  - Tachycardia
  - Respiratory distress
  - Petechiae
  - Ecchymosis
  - Jaundice
- The rash associated with TSS
  - Diffuse macular erythema that may resemble sunburn
  - Often involves both the skin and mm, includes the palms and soles
  - May be transitory
- Patients with streptococcal TSS often have an identifiable focus on examination
- Vaginal examination may reveal
  - Hyperemia
  - Tampons
  - Other foreign bodies

Diagnostic testing

1- **Blood cultures**
   - Positive in < 5% of cases of staphylococcal TSS
   - Positive in about 60% of cases of streptococcal TSS

2- **Mucosal or wound cultures**
   - Positive in up to 90% of patients with staphylococcal TSS

3- Laboratory studies will show signs of **multiorgan failure**

Diagnostic criteria for staphylococcal TSS

1- **Fever** ≥ 38.9 C

2- **Rash** : diffuse macular erythroderma

3- **Desquamation:**
   - Occurs 1-2 weeks after onset of illness, especially palms and soles

4- **Hypotension**
   - Systolic Bp ≤ 90 mmHg
   - Orthostatic decrease in diastolic Bp ≥ 15 mmHg

5- **Multisystem involvement (≥ 3 systems)**
   - Gastrointestinal: vomiting or diarrhea
   - Muscular: severe myalgia or creatine kinase > 2X normal
   - Mucous membranes: vaginal, oropharyngeal, conjunctival hyperemia
   - Renal: BUN or creatinine > 2X normal, pyuria
   - Hepatic: total bilirubin > 2X normal
   - Hematological: platelets ≤ 100,000μ/L
   - CNS: disorientation or alteration of consciousness without focal neurological signs

6- **Negative results** of blood, throat or CSF cultures (blood cultures may be S.aureus positive) and **no rise of antibody titers** against R. rickettsii, Leptospira spp.and rubeola

■ Confirmed cases → satisfies all 6 criteria

■ Probable cases → satisfies 5 of 6 criteria

Diagnostic criteria for streptococcal TSS

1- **Hypotension**

- Systolic Bp ≤ 90 mmHg

2- **Two or more of the following**

- Renal impairment: creatinine ≥ 2 mg/dl
- Coagulopathy: platelets ≤ 100,000μ/L or DIC
- Hepatic involvement: transaminases or bilirubin > 2X normal
- Generalized erythematous macular rash that may desquamate
- Adult respiratory distress syndrome
- Soft tissue necrosis (necrotizing fasciitis, pyomyositis)

■ Confirmed case includes: isolation of S.pyogenes from a normally sterile site (blood, CSF, peritoneal fluid and tissue biopsy) in addition to satisfying both criteria

■ Probable case includes: isolation of S.pyogenes from a nonsterile site (throat, skin and vagina) in addition to satisfying both criteria

Differential diagnosis

1- Systemic infections as gram negative sepsis including meningococcemia

2- Rocky Mountain spotted fever

3- Leptospirosis [in previously healthy individuals]

Treatment

1- Appropriate cell wall acting antibiotic + clindamycin

2- **Empiric choice for staphylococcal TSS** should include an agent that is effective against MRSA

- Vancomycin is the typical first choice
- Possible alternatives: linezolid, daptomycin and telavancin
- If S.aureus is found to be methicillin sensitive , give oxacillin or nafcillin

3- **Empiric choice for streptococcal TSS**

- Penicillin

4- **Clindamycin**

- Effect: it binds to the 50S ribosomal subunits and prevents peptide bond formation so, halt toxin production and arrest disease progression
- If clindamycin contraindicated, linezolid is an alternative that also arrests toxin production in vitro

5- **Intravenous immunoglobulin (IVIG)**

- It cantains neutralizing antibodies against many of the superantigens implicated in causing both syndromes
- Studies have failed to show significant improvement in patients treated with IVIG due to small sample sizes, but it is generally used, especially if patients are not responding to therapy

6- **Duration of antibiotic treatment**

- At least 14 days
- But depends on clinical response, the presence or absence of a focus of infection and associated bacteremia

7- Extensive fluid resuscitation is often required

8- Vasopressors and mechanical ventilation may be necessary

9- Aggressive debridement of any focus of infection, including SSIs is important

10- Multiorgan failure is common → ICU management

Prognosis

1- **Menstrual staphylococcal TSS** has the best prognosis → mortality rate < 2%

2- **Nonmenstrual staphylococcal TSS** → has mortality rate of up to 5%

3- The mortality rate for **streptococcal TSS** remains high → about 40-60%

4- **Recurrences** of TSS are possible and occur in 1/3 of patients with menstrual type

Bacillary dysentery

Etiology

1- **Causative organism**

- Non motile gram negative shigella bacilli which belonging to the family Enterobacteriaceae
- There are 4 groups
  - Shigella dysenteriae → tends to cause epidemics
  - Shigella flexneri → commonly causes endemic dysentery in developing countries
  - Shigella bodii → common on the Indian subcontinent
  - Shigella sonnei → is an important cause of dysentery in the industrialized world

2- **Source of infection**

- Asymptomatic carriers (humans are the only important reservoir)

3- **Mode of infection**

- Feco-oral via flies, food, water and person-person contact including various sexual practices

4- **Shigellae** are notably resistant to gastric acid and a very small ingested dose as few as 10 bacilli may cause clinical disease

5- **Pathogenesis**

- Shigellosis principally affects the colon and sometimes, the terminal ileum
- Clinical manifestations caused by combination of enteroinvasion and toxin production
- Shiga toxin an exotoxin produced by certain strains of S. dysenteriae type 1 consists of
  - An enterotoxin → secretory diarrhea
  - A cytotoxin → cell necrosis
  - A neurotoxin → CNS complications in children
  - May be involved in the pathogenesis of HUS

Clinical features

1- Age → children < 5 years (70% of cases)

2- I.P. → 1-8 days (5 days)

3- Asymptomatic

4- Mild and self limiting attacks

- Characterized by watery diarrhea without blood or mucus which resolve spontaneously after a few days

5- Severe disease

- Usually caused by Sh. dysenteriae and Sh. flexneri (Sh. Sonnei usually milder but may be severe in infants)
- Abrupt onset of bloody mucoid stools, cramps, tenesmus
- Often accompanied by fever, malaise and sometimes dysuria and confusion
- Nausea, vomiting and headache may occur
- Fever, confusion, meningism and convulsions often precede the onset of diarrhea in young children

6- Fulminating gangrenous infection

- Caused by Sh. Dysenteriae type 1
- Abrupt onset of fever, chills, rigors, vomiting and toxaemia
- The patient can pass 20-60 bloody stools per day often containing mucus and pus and sometimes even sloughs of mucosa
- Perforation is relatively rare, but severe dehydration, blood loss and sepsis can lead to acute renal failure

7- Choleraic form

- Rarely, with abrupt onset of profuse watery diarrhea that later becomes bloody and is associated with high mortality

8- Complications

- HUS: occurs in 13% of cases of Sh. Dysenteriae type 1 usually 1-5 days after the onset of dysentery
- Toxic megacolon

- Post dysenteric colitis and strictures
- Protein losing enteropathy
- Granular proctitis, piles, parotitis
- Rectal prolapse in children
- Post dysenteric Reiter's syndrome (symmetrical arthritis, conjunctivitis and urethritis) is a well recognized sequela

9- Differential diagnosis

- Other causes of dysentery or bloody stools

Investigations

1- Stool analysis and culture:

- Stools often described as like "redcurrant jelly"
- Excess pus cells and RBCs with scanty bacilli
- Stool culture even if the sample is fresh, is often difficult and rectal swabs are more likely to be +ve esp. if directly inoculated onto appropriate culture media at the bedside

2- Sigmoidoscopy

- The colonic mucosa is red and swollen with pseudomembrane

Treatment

1- Oral rehydration solution → in most cases is sufficient

2- Fluid replacement

- In more severe cases
- I.V. fluids as normal saline ± K depending on renal function or ringer's lactate solution
- Blood transfusion may be indicated
- Patients with HUS may require dialysis

3- Antibiotics

- The WHO recommends that all cases of bloody diarrhea should be treated promptly with an effective antibiotic
- 1st choice → ciprofloxacin 500 mg twice daily or another fluoroquinolone

- 2nd choice → pivmecillinam, ceftriaxone or azithromycin
- The use of antibiotics in children with dysentery caused by E.coli 0157:H7 which produces a shiga like toxin is associated with increased risk of HUS. However, this association has not been demonstrated among patients with shigellosis
- 2ry septicemia from gut anaerobes and other enteropathogens should be considered in severely ill patients

4- Zinc and vitamin A supplement

- Daily zinc supplements are recommended for 10-14 days in children < 5 years
- Vitamin A also reduces the incidence and severity of episodes of diarrhea including dysentery

5- Avoid

- Drugs that decrease intestinal motility and antispasmodics are better to be avoided as they may decrease the intestinal wash of the organisms

Antibiotic associated diarrhea/colitis

Etiology

1- C.difficile

- Spore forming gram +ve obligate anaerobe that is present in 3% of healthy adults
- Colonization rates are 10% to 30% of hospitalized patients
- Should be suspected in any patient who has diarrhea in association with antibiotic exposure

2- Risk factors

- Exposure to antimicrobial agents (the most important)
- Advanced age
- Hospitalization
- Cancer chemotherapy
- GI surgery
- Manipulation of the GI tract such as tube feeding and acid suppressing medications

3- Mechanism

- CDI results in acute inflammation of the colonic mucosa
- Disease results from spore germination, colonization, overgrowth and toxin production
- Pathogenic strains produce toxin A and B or B alone
- During infection, only the epithelium and the superficial lamina propria are affected, although in more severe cases, deeper tissues are involved
- **Pseudomembranes** may be found throughout the colon but are worst in the **rectosigmoid region**
- The ileum is rarely involved unless there is a previous colostomy/ileostomy

Clinical features

1- Symptoms usually beginning **4-10 days after starting antibiotic therapy** (range 24 h to 8 weeks)

2- Profuse watery or green mucoid, foul smelling **diarrhea**

3- Cramping **abdominal pain**

4- The stool may be +ve for **occult blood**

5- **Complications**: Patients may develop toxic megacolon, perforation, peritonitis and hypotension or shock

Differential diagnosis

1- **Osmotic diarrhea from antibiotic use**

- More common than CDI, but not associated with fever or leukocytosis

2- Crohn's disease, ulcerative colitis and ischemic colitis

3- **Other intestinal pathogens as**

- E.coli
- Salmonella spp.
- Campylobacter spp.
- Yersinia spp.
- E.histolytica
- Strongyloides

Investingations [diagnosis based on detection of C.difficile toxin]

1- **Culture**

- Followed by detection of toxigenic isolate is the gold standard but takes up to 4 days

2- **Toxin assay**

- Cytotoxicity cell assays detecting toxin B
- Enzyme immunoassay detecting toxin A and B or toxin A
- PCR detecting toxin A or B
- Because of the minimal increase in yield and false +ve results, repeat testing of multiple stools is not recommended

3- **C.difficile common antigen glutamate dehydrogenase (GDH)**

- Present in all strains but testing for it must be followed by toxin assay
- Nontoxigenic strains do not cause CDI and other bacteria also produce GDH

4- **Endoscopy**

- May be useful, but pseudomembranous colitis is seen in only about 50% of patients with CDI

Treatment

1- Offending antibiotics should be **stopped** when possible

2- Summary of treatment options

Type of CDI	Criteria	Treatment
Mild to moderate and 1st or 2nd episode	----------	Metronidazole 500 mg PO q8h for 10-14 days
≥ 3rd episode	----------	Vancomycin 125 mg PO q6h for 10-14 days, considering tapering or pulsed regimen
Severe	Leukocytosis with > 15,000 cells/µL or creatinine ≥ 1.5 times the premorbid level	Vancomycin 125 mg PO q6h for 10-14 days
Severe and complicated	Ileus, megacolon, pending perforation, hypotension or shock	Vancomycin 125-500 mg PO q6h or vancomycin enema + metronidazole 500 mg IV q8h. request surgical consult

3- An example of tapering vancomycin regimen

- 125 mg PO tid for 1 week
- Then 125 mg PO bid for 1 week
- Then 125 mg PO once daily for 1 week
- Then 125 mg PO 3 times a week for 2-8 weeks

Food poisoning

Causes

1- Infective

- Non toxin mediated
  - Salmonella
  - Bacillus anthracis (anthrax)
  - Helicobacter
  - Listeria causing meningitis
- Toxin mediated
  - Staph aureus
  - Botulism
  - E.coli (enterohemorrhagic)

2- Non infective

- Allergic
  - Shellfish
  - Strawberries
- Non allergic
  - Chemicals and metals (in cooking pots)

Comparison of types of food poisoning

Organism	I.P. (hrs)	C/P	Pathogenesis	Type of food	Outcome
Staph. Aureus	1-8	Vomiting & diarrhea	Enterotoxin in food	CHO, milk & milk products	Recovery in 1-2 days
Salmonella typhimurium & Enteritidis	12-48	Vomiting, diarrhea and fever	Multiplication in gut No toxin	Infected meat or eggs	Treatment may be needed
Cl. Botulinum	18-24	Neurologic	Neurotoxin in food	Canned food	High mortality rate
Cl. Perfringens	6-18	Diarrhea	Multiplication & enterotoxin	Reheated meat dishes	Recovery in 1-2 days
B. cereus Emetic type Diarrhoeal type	 1-5 8-24	 Vomiting Diarrhea	 H.s enterotoxin H .L enterotoxin	Reheated cooked rice Meat & sauces	 Recovery in few days
V. parahaemolyticus	6-30	Vomiting, diarrhea & fever	Multiplication in gut & haemolysin	Contaminated sea food	Recovery in few days
L. monocytogenes	8-48	Diarrhea & fever	Multiplication & invasion	Cheese & undercooked meat	Recovery in few days

Cholera

Definition

1- It is an acute infectious **epidemic disease** characterized by

- Profuse purging and vomiting of colourless watery material
- Muscular cramps
- Suppression of urine, algidity and collapse
- The presence of vibrios in the intestine

2- It is associated with a **high mortality rate**

Etiology

1- There are 3 types of vibrios

- Cholera vibrios (Ogawa, Inaba and Hikojima)
- El-Tor vibrios
- Non agglutinable vibrios

2- Mode of transmission

- Feco-oral [Direct faecal contamination of food and water and infection is by the oral route]

3- Mechanism

- In the intestine, cholera enterotoxin activates the production of adenyl cyclase catalyzing transformation of adenosine triphosphate (ATP) to cAMP
- This activation of cAMP leads to increased secretion of fluid and abnormal ion transport from the plasma to intestinal lumen leading to hypovolemic shock and metabolic acidosis
- There is no cell denudation or increase in mucosal intestinal permeability

Clinical features

1- **WHO suspected case definition**

- In an area where cholera is not endemic → severe dehydration or death from watery diarrhea in a patient aged ≥ 5 years
- In an area where there is a cholera epidemic → acute watery diarrhea ± vomiting in a patient aged ≥ 5 years

2- **I.P.** → 1-6 days (the shorter the I.P. the more severe the disease)

3- **Main features**

- Painless diarrhea, profuse colourless rice water stools
- Vomiting is copious with no nausea and gushes out with flecks of mucus
- Patient looks ill but alert
- Usually manifestations of dehydration

4- **Grades**

- Grade 0 → no symptoms except few motions of watery diarrhea
- Grade 1 → watery diarrhea and thirst. Fluid loss < 5% of the body weight
- Grade 2 → like grade 1 but fluid loss is 5-7.5% of body weight, tachycardia, systolic blood pressure 80-100mmHg and markedly diminished urine output
- Grade 3 → diarrhea is continuous and is associated with vomiting. Fluid loss up to 10% of body weight. There is hypovolemic shock, weak rapid pulse, systolic pressure < 80 mmHg, sunken eyes, markedly diminished skin turgor, cold extremities, muscular cramps and anuria
- Grade 4 → fluid loss > 10% of body weight. Patient comatose with imperceptible pulse, immeasurable blood pressure and rapid deep respiration. Cramps in the limbs and abdomen are due to decreased chlorides and calcium. There may be decrease in urine output or even anuria

5- Other clinical types

- Ambulatory case → in which frequent loose stools is the main complaint
- Typhoid cholera → in which febrile state is aggravated
- Cholera sicca → in which collapse sets early with little or no diarrhea and the condition is mostly fatal

Diagnosis

1- Clinical

- During epidemic → acute onset, frequent painless watery stools, normal or subnormal temperature and manifestations of dehydration

2- Bacteriological diagnosis

- First case in a non endemic area
  - Any comma shaped motile organisms detected in a stool sample from the first case suspected to be cholera in a non endemic area should be thoroughly identified before giving a report as + ve for cholera
  - Required to confirm the diagnosis and to determine the serogroup and serotype for epidemiological purposes
  - Cholera vibrios can survive for several days in alkaline peptone water or Cary Blair medium for transport to a laboratory distant from the epidemic
  - Specimens taken by rectal swab are cultured at 37 C on thiosulphate citrate bile sucrose (TCBS) agar
  - V.cholerae colonies are identified by

    © A wet mount which is examined for the characteristic darting motility

    © Smears stained with gram stain show gram negative comma shaped bacilli

    © Produces characteristic yellow oxidase positive colonies that can be tested for agglutination with 01 or 0139 anti sera
  - Recently, immunodiagnostic dipsticks have been developed for rapid diagnosis

- 2ry case during an epidemic
    - In an established epidemic, cases can be diagnosed by microscopic examination of stools for comma shaped bacilli with characteristic darting motility (single terminal flagellum) which can be immobilized bt adding specific anti-O cholera sera

3- Direct methods

- Can detect V. cholerae O1 and O139 in stools as fluorescent antibody staining, coagglutination and immunoassay
- PCR for detection of cholera toxin genes is available

4- Blood examination

- Leucocytosis with ↑ RBCs count
- Usually low Na, high K, low calcium, acidosis and rise of blood urea

Differential diagnosis

1- Food poisoning

- History of several persons having been attacked at the same time
- Violent and distressing vomiting which precedes diarrhea
- Severe abdominal pain with greenish offensive stools
- Urine output is never suppressed
- Fever and headache are usually present and leucocytosis is absent

2- Acute bacillary dysentery

- Sudden onset of fever, chills, abdominal colic and frequent passage of mucous and blood, sigmoid is tender

3- Acute trichinosis

- Fever, diarrhea and severe muscular pains
- Leucocytosis and high eosinophilia are usual

Treatment

1- **Initial I.V. rehydration and correction of electrolyte imbalance**

- The mainstay of cholera treatment
- In all patients with hypovolemic shock the initial fluid deficit will be at least 10% of the body weight → it is a safe rule of thumb to give 1/3 of the total estimated deficit in the first 20-30 min
- Ringer's lactate solution
    - The single fluid that meets all needs as such patients usually have metabolic acidosis as a result of bicarbonates loss, a deficiency of K and a loss of water greater than salts
- Initial rate of 4 L/h for the first few litres is the norm in adults then 1 L every 30-45 min
- Children in shock should receive i.v. fluids at a rate of 40 ml/kg/body weight over the first 30 min through scalp or external jugular veins
- The best guide to success
    - Return of a palpable arterial pulse (60-100/min)
    - Return of conscious level
    - As soon as the systolic blood p[ressure reaches 90 mmHg, renal function usually returns
- Overrehydration is manifested by
    - Irritability
    - Dyspnea
    - Puffiness of eyes
    - Congested neck veins, rapid full pulse
    - Finally signs of pulmonary edema

2- **Maintenance hydration**

- Fluid losses are estimated 8 hourly and replaced plus 500 cc daily
- Once the patient is rehydrated and able to take fluids by mouth, oral rehydration should begins, although diarrhea may be continuing
- Oral rehydration with glucose electrolyte solution is used for:

- Maintenance hydration in severe cases following resuscitation or
- For all milder cases from the beginning

- Oral rehydration should initially be given frequently and in small amounts

3- Antimicrobial therapy

- Drugs
  - Tetracycline 500 mg 6 hourly for 3 -5 days-
  - Furazolidone 400 mg/day for 3 days
  - Single dose of doxycycline 300 mg
- Effect
  - Reduce the volium and duration of diarrhea esp. in those with severe disease
- Resistance
  - Frequently reported esp. to tetracycline and indiscriminate use for mild cases should be discouraged → use chloramphenicol or sutrim

4- Isolation of hospitalized patients

- Single rooms with toilet facillites and standard barrier precautions are necessary
- Use of chlorine based disinfectants after discharge is also necessary

5- Discharge

- 3 rectal swabs are taken at 8, 9 and 10 day of admission (3 successive days)
- +ve cases are discharged from the hospital 2 days after the 3rd negative stool culture

6- Carriers

- Treated by tetracycline 500 mg orally every 6 h for 3 days

Prevention

1- Oral cholera vaccines

- Whole cell B subunit vaccine (WC-B vaccine)
  - Combines purified B subunit and killed whole cells
  - Licensed for use in UK for travelers to cholera endemic areas esp. those who may be working with refugees or going to remote areas
  - The vaccine produce B subunit that binds to specific receptors on the intestinal mucosal cells and is responsible for cholera organisms immunogenicity
- Genetically engineered vaccine (103HgR)
  - Live attenuated vaccine which protects against the cholera enterotoxin
- An extract of killed bacteria → given in 2 i.m. doses with one week interval

2- Chemoprophylaxis

- Current WHO recommendations do not support the use of antimicrobials (tetracycline) as prophylaxis against cholera in endemic or epidemic situations

Tetanus

Causative organism

1- **Clostridium tetani**

2- Gram +ve bacilli, obligate anaerobe with a terminal spore, which is ubiquitous in the environment, esp. in soil [present also in street dust, human and animal faeces]

3- Spores are highly resistant to light and temperature

Mode of infection → inoculation of spores into wounds (usually acute injuries)

Pathogenesis

1- **Spores germinate under anaerobic conditions** at the site of the wound and the growing bacteria produce 2 exotoxins: Tetanolysin and tetanospasmin

2- **Tetanospasmin:**

- Undergoes proteolytic cleavage and binds and enters the presynaptic terminal → then it cleaves the protein that allows fusion of synaptic vesicle with the membrane and thus prevents transmitter release
- It is able to travel retrogradely via axons to cell bodies and and crosss synapses → thus reaching the spinal cord, brain and autonomic nervous system
- It primarily affects inhibitory GABA neurons → leading to increased firing and lack of normal relaxation causing the classical spasms of tetanus

3- **Tetanolysin:**

- Causes lysis of the erythrocytes and kills neutrophils

4- The disease is subdivided to classical clinical subtypes which reflects the main site of action of toxin

Clinical features

1- **Incubation period**

- Variable according to the site of injury and is shorter in severe disease
- Average I.P. for severe disease → 8 days

2- Generalized tetanus

- The most common clinical form
- Prodromal symptoms: often precede muscle spasm by 24 hr and take the form of restlessness, irritability and neck stiffness
- Tonic rigidity
    - Trismus (lock jaw) in which the patient is unable to open his mouth (due to spasm of masseter muscles) → the first indicator of tonic rigidity and the first symptom beginning as slight painful stiffness in the jaws or
    - Risus sardonicus (sad smile), which is a grimace caused by spasm of facial muscles
    - Rigidity of the abdominal and erector spine muscles begin to appear. Abdominal wall becomes hard to palpate
- Repeated spasms which may involve the neck, thorax, abdomen or extremities
    - The predominant feature, and may lasts for minutes
    - Precipitated by external or internal stimuli
    - Painful as full consciousness is retained
    - Difficulty in breathing and swallowing due to laryngeal and pharyngeal spasms
- Generalized spasms with opisthotonos also occur
- Respiratory compromise:
    - May occur because of involvement of the glottis or diaphragm
- Autonomic dysfunction:
    - May occur after several days in severe cases
    - Difficult to manage, as manifestations can alter quite rapidly
    - Hypertension, hyperpyrexia
    - Tachycardia and arrhythmias

- Prognosis
    - The disease may continue to progress for up to 10 days after the first symptoms and recovery may take up to 4 weeks
    - Cause of death → usually, respiratory compromise or Autonomic dysfunction
    - Case fatality rates → 60%

3- Localized tetanus

- Usually a mild form
- Rigidity and weakness is limited to muscles near the site of injury (weakness may occur because of the action of the toxin at the neuromuscular junction)
- Prognosis
    - Symptoms may persist for months
    - If the diagnosis not made → progression to the generalized form may occur

4- Cephalic tetanus

- It is the rarest form
- Occurs in head injuries or with middle ear infection
- I.P. → 1-2 days
- Major clinical manifestations due to involvement of cranial nerves
- Clinically:
    - Facial paresis
    - Extraocular palsies
    - Dysphagia
- Prognosis → may progress to generalized type

5- Neonatal tetanus

- Cause → infection of the umbilical stump
- Risk factors
    - Length of the cord
    - Equipment used to ligate and cut the cord
    - Environment

- Occurs only in the neonates of non-immune mothers
- Onset → 1-10 days postpartum
- Initially
    - Generalized weakness and floppiness
    - Irritability
    - Inability to suck and feed however he is still able to cry & take milk with spoon.
- Subsequently
    - Spasms
    © Both suckling and drinking become impossible due to spasm of pharyngeal muscle, infant becomes unable to cry
    © Later, spasm of respiratory muscles is accompanied by severe apnea & cyanosis
    - Opisthotonos and hypertonia
    - Hypersympathetic states
- Prognosis
    - 90% of affected infants die
    - Mental retardation is common in survivors

Diagnosis

1- Usually clinical

2- Bacteriology is of little help; the organism often not found and a positive wound culture for Cl. Tetani does not prove that the organism is toxin producing and causing disease

3- Blood and CSF findings are usually normal

Differential diagnosis

1- Local causes of trismus

- Quinsy
- Dental abscess
- Mumps
- [Fever + local pain + enlarged tender cervical L.N]

2- **Meningitis and encephalitis**
    - Neck and back stiffness may be similar, but in tetanus patient is fully conscious and well oriented until the end
3- **Strychnine poisoning:** spasms are simillar but in strychnine muscles become flaccid between the attacks
4- **Dystonic reactions**
5- **Hypocalcemia and seizures in adults**
    - Tetany affecting the hands causing carpopedal spasms but hands are free in tetanus
6- **Metabolic or neurological causes** of posturing in neonates
7- **Rigid abdomen** in peritonitis
8- **Malingering:** may take the form of lock jaw but during sleep, muscles relax completely

Complications

1- Respiratory: pneumonia, atelectasis, pulmonary edema & respiratory failure.
2- Cardiac: tachycardia, arrhythmia, hypotension and heart failure.
3- Neurological: 5th, 7th, 10th and 12th cranial nerve affections.
4- GIT: acute peptic ulceration, paralytic ileus and constipation.

Treatment

1- **Avoidance of external stimulation**
    - Isolation in a quiet dim room
    - Gentle manipulations
2- **Protection of the air way**
    - Endotracheal intubation and tracheostomy is often necessary
3- **Ryle gastric tube & urinary catheter** insertion is important
4- **Fluids & rehydration measures**
5- **Neutralization of toxins** → Tetanus immunoglobulin
    - Human → 150 iu/kg I.M or

- Equine → 10^4 -10^6 iu I.M [40.000-80,000 units for adults & 20,000 for infants, injected intramuscularly after testing for sensitivity is performed]

6- <u>Eradication of the bacteria</u> → to prevent multiplication

- Metronidazole or
- Benzylpenicillin: 1 milion IU/6 hours for 5 days

7- <u>Surgical debridement of the wound</u> → and cleaning with hydrogen peroxide to prevent further germination of spores

8- <u>Control of spasms</u>

- High doses of benzodiazepines
- Baclofen also effective
- Paralysis with non-depolarizing neuromuscular junction blockers may be required in some patients

9- <u>Treatment of autonomic instability</u>

- Labetolol or verapamil for HTN
- Atropine or pacing for bradycardias
- Sympathomimetics and fluids for hypotension

10- <u>I.V. magnesium</u> → ↓↓ the need for muscle relaxants and drugs to control cardiovascular manifestations

Prophylaxis of tetanus

1- <u>DPT vaccine</u> [tetanus toxoid]

- At 2, 4, 6 months
- Boosters at 4-7 yr and in adolescence
- Then, A single booster in adulthood → lifetime protection

2- <u>Pregnancy</u>

- 2 doses 4 weeks apart during the 2nd trimester

3- <u>In tetanus prone injuries</u>

- Booster dose should be given if not immunized within the last 5 years

4- <u>For those first vaccinated in adulthood</u>

- Routine booster doses at 10 yearly intervals following 1ry immunization [5 doses in total protects for life]

Plague

Etiology

1- Zoonotic disease primarly affecting rats and rodents

2- Causative organism:

- Yersinia pestis
- Gram negative non spore forming coccobacillus
- When stained by Wayson stain, they show marked bipolar staining (Safety pin appearance)
- Colonies surfaces show hammered metal appearance

3- Mode of transmission

- Mostly by bite of rat flea Xenopsylla cheopis
- Rarely, by direct contact of plaque infected material in an open skin lesion
- Pneumonic disease can be transmitted from person to person and would be expected after inhalation of aerosolized Y.pestis
- Dissemination of the disease occurs through transportation of infected rats in ships

Clinical forms

1- Bubonic plague

- It is the classical disease in man
- I.P. → 2-6 days
- Sudden onset of fever, shaking chills, headache, severe malaise and pains in the affected regional lymph nodes which may not be clinically enlarged at this stage
- Regional lymphadenitis (bubo) enlarge rapidly and become palpable, flactuant and painful with limitation of motion
- Lymph nodes affected are: inguinal, axillary, supraclavicular, cervical, intraabdominal and intrathoracic in this order of frequency
- Extensive perinodal inflammatory reaction may occur

- Eyes and face are usually injected

2- Septicemic plague

- It is the most dangerous type
- Usually from progression of bubonic disease
- A characteristic bubo either does not develop or it develops in the deeper lymphatics undetectable by palpation
- Fever, chills, severe prostration, hypotension, peripheral necrosis and manifestations of DIC (i.e. Black death) are usual
- Meningitic and encephalitic symptoms may occur

3- Pneumonic plague

- Has a short incubation period (1-3 days)
- Influenza like illness (high fever, chills) followed by severe pneumonia with cough and bloody sputum
- The condition may be secondary to bubonic or septicemic types

4- Pestis minor

- It is a benign form of plague
- Characterized by the occurrence of buboes and absence of toxicity

Diagnosis

1- Compatible epidemiological and clinical features

2- CBC → usually shows leucocytosis with PMN predominance

3- Confirmation is done by **isolation of Y.pestis** from aspirates of the buboes, blood, CSF and sputum

- Material for culture is injected into a tube containing peptone broth with penicillinase
- The organism is identified by microscopic morphology and biochemical reactions

4- Direct detection of the **capsular F1 antigen** in specimens by immunofluoresence technique (2-3h) or detection of **DNA by PCR**

5- Serological diagnosis by ELISA or passive haemagglutination

- Useful mainly in convalescent stage

- The presence of a rising antibody titre is diagnostic

Treatment

1- Should be **started at first suspicion** of plaque because rapid initiation of antibiotics improves survival

2- Isolation of the patient is essential particularly if pulmonary involvement has not been ruled out

3- Drugs of choice are

- Streptomycin 1g IM q12
- Gentamicin 5 mg/kg IV/IM daily or a 2 mg/kg loading dose, then 1.7 mg/kg IV/IM q8h with appropriate monitoring of drug levels
- Doxycycline 100 mg PO/IV bid

4- Alternative drugs

- Ciprofloxacin and chloramphenicol

5- Duration of therapy

- Oral therapy can be started after clinical improvement for a total course of 10-14 days

6- In septicemic cases

- Streptomycin plus doxycycline are used

7- Postexposure prophylaxis (contacts)

- Doxycyline 100 mg PO bid or
- Ciprofloxacin 500 mg PO bid for 7 days after exposure

8- Prevention

- Strict quarantine measures against ships coming from foreign parts by fumigation to kill rats
- Using rodenticide (warfarin)
- لا تبدأ حملات القضاء على الطاعون بالتخلص من الفئران لأن البراغيث ستهاجم الانسان بدلا من الفئران

VIRAL DISEASES

	Family	Representative viruses
RNA viruses	Picornaviridae	Poliovirus
		Coxsackie virus
		Echovirus
		Enterovirus
		Rhinovirus
		Hepatitis A virus
	Caliciviridae	Norwalk agent
		Hepatitis E virus
	Togaviridae	Rubella virus
		Eastern equine encephalitis virus
		Western equine encephalitis virus
	Flaviviridae	Yellow fever virus
		Dengue virus
		West Nile virus
		Hepatitis C virus
	Coronaviridae	Coronaviruses
	Rhabdoviridae	Rabies virus
	Filoviridae	Marburg virus
		Ebola virus
	Paramyxoviridae	Parainfluenza virus
		Respiratory syncytial virus
		Newcastle disease virus
		Mumps virus
		Rubeola (measles) virus
	Orthomyxoviridae	Influenza A, B, and C viruses
	Bunyaviridae	Hantavirus
		Sandfly fever virus
		Rift Valley fever virus
	Arenaviridae	Lymphocytic choriomeningitis virus
		Lassa fever virus
		South American hemorrhagic fever virus
	Reoviridae	Rotavirus
		Reovirus
		Colorado tick fever virus
	Retroviridae	Human T-lymphotropic virus types I and II
		Human immunodeficiency virus types 1 and 2
DNA viruses	Hepadnaviridae	Hepatitis B virus
	Parvoviridae	Parvovirus B19
	Papovaviridae	Human papillomaviruses
	Adenoviridae	Human adenoviruses
	Poxviridae	Variola (smallpox) virus
		Orf virus
		Molluscum contagiosum virus
	Herpesviridae	Herpes simplex virus types 1 and 2 (called human herpesvirus (HHV) 1 and 2)
		Varicella-zoster virus (Also called HHV-3)
		Epstein-Barr virus (Also called HHV-4)
		Cytomegalovirus (Also called HHV-5)
		Human herpesvirus 6
		Human herpesvirus 7
		Kaposi's sarcoma–associated herpesvirus (Also called HHV-8)
	Polyomaviruses	JC virus
		BK virus

Infectious mononucleosis (Glandular fever)

Pathogenesis

1- **Causative organism** → there is association of I.M and EBV which is a herpes virus [restricted to B lymphocytes]

2- **Mode of transmission**

- Oral route, as the virus is isolated from saliva, throat, washings, also in squamous epithelium of cervix
- Sexual transmission
- Blood transfusion in seronegative individuals

3- **Distribution**

- The virus affects all population
- The disease is more common in high than low socioeconomic groups

4- **Histopathology**

- Excision biopsy is rarely done except in complicated cases
- Findings may mimic B cell lymphoma → mononuclear cell infiltrate with immunoblastic appearance

5- Manifestations are related to **lymphoproliferation** which is self limited

6- **The course of EBV** depends on

- Genetic susceptibility of the host
- Status of humoral and cellular immunity at the time of infection
- An endogenous RNA tumor virus
- Involvement of virulent virus strains

Clinical features

1- Incubation period → 4-6 weeks

2- **Symptoms**

- Fatigue, malaise and myalgia for 1-2 weeks
- Fever → low grade for 2 weeks, may be up till 1 month
- Sore throat

3- Signs

- Lymphadenopathy
    - Mainly posterior cervical and may be generalized
    - Tender, symmetrical and not fixed
- Pharyngitis and tonsillar enlargement
- HSM, rarely jaundice

4- Complications

- It is a self limited disease (6-8 weeks)
- Sometimes, relapse occur within 6 months
- Rare complications
    - Acute liver necrosis
    - Splenic rupture
    - Pharyngeal obstruction
    - Neurological complications
    - Autoimmune thrombocytopenia
    - Haemolytic anaemia

5- 2ry EBV may be associated with

- Burkitt's lymphoma
- Nasopharyngeal carcinoma
- Mixed cellularity type of Hodgkin's lymphoma

Differential diagnosis

1- Viral LN

2- Acute leukemia

3- Acute hepatitis → prodromal arthralgia, rash, ↑ bilirubin

4- Systemic disease

- Endocarditis
- Lymphoma and leukemia

Diagnosis

1- **Blood picture**

- Atypical lymphocytes forming 30% of the mononuclear lymphocytes
- This findings occurs also in
  - Other mononucleosis syndromes
  - Viral hepatitis
  - Mumps

2- **High titers of heterophilic antibodies (IgM)** which can aggluniate sheep or horse erythrocytes

- Monospot test
  - It is a haemagglutination test using treated horse erythrocytes for the heterophilic antibodies associated with infectious mononucleosis
  - Positive test results must be accompanied by typical clinical signs and symptoms
- Paul-Bunnell test
  - It detects IgM heterophilic antibodies which agglutinate sheep or horse erythrocytes
  - Differentiated from heterophilic antibodies associated with other disease by their significant absorption to ox erythrocytes, but not guinea pig kidney
  - A titre > 1/448 is diagnostic

3- **ELISA for EBV**

- It depends on detection of specific antibodies against EBV specific antigens

4- **In case of hepatitis**

- ↑ serum bilirubin and transaminases
- ↓ serum albumin

5- **Isolation** of the virus from the throat

6- **Specific antigens**

- Viral capsid antigens (VCA) → recent infection have IgM, IgG to VCA – IgG persist for years
- Early antigen (EA) → antibodies persist for months in 85% of cases
- EBNA (EB nuclear antigen) → arise weeks after infection and persist for life
- Membrane antigen (MA): antibodies as EBNA
    - Recent infection : diagnosed by VCA (IgM), EA antibodies
    - Past infection: titre 1/320 or rising titre (VCA –IgG-) and EBNA antibodies
- EBV protein by immunoflorescence technique: not routinely done
- Specific RNA, DNA sequence by southern blot hybridization
- PCR for DNA in blood and tissues

Treatment [self limited disease]

1- Rest to avoid splenic rupture

2- **Symptomatic** treatment

3- **Avoid ampicillin** for the fear of skin rash

4- **Prednisolone**

- Dose : 40-60 mg for 2-3 days and reduce the dose over 1-2 weeks
- Indication
    - Pharyngeal edema
    - Autoimmune haemolytic anemia
    - Thrombocytopenia

Causes of spleen liable to rupture [Don't examine or gentile palpation]

1- Malaria

2- Sequestration crises of haemolytic anemia

3- Infectious mononucleosis

4- Certain types of lymphoma

Acquired cytomegalovirus infection

Pathogenesis

1- **Causative organism**

- It is caused by herpes group virus which is a double stranded DNA
- It is a protein capsid with lipoprotein envelop

2- **Source of infection**

- Infection is acquired from asymptomatic chronic excretors through prolonged close contact
- Virus is excreted in saliva, urine, semen, cervical, milk secretion and post-transfusional
- So, primary infection occurs through blood, while reactivation of latent virus occurs among immunosuppressed, esp. in transplantation

3- Complications as hepatitis etc. are due to virus **cytopathic effect** on organs

4- The majority of **immunocompetent** individuals who are acutely infected with CMV experience **no symptoms**

Clinical features

1- Incubation period → 30-60 days

2- **Influenza like** for ≥ 2 weeks

3- **Hepatomegaly** is common

4- Pharyngitis, tonsillitis and lymphadenopathy are less common

5- **Neurological conditions**

- Polyneuritis may occur
- Polyradiculopathy affecting lumbosacral roots leading to
  - Paraparesis
  - Sphincteric disturbance

6- **In children and adults cause**

- Asymptomatic infection
- Subclinical infection
- Mononuclear syndrome
- Disseminated in immunocompromised

Clinical types

1- **Congenital**

- Either inapparent or develop
- Petichae, HSM, jaundice, intrauterine growth retardation or prematurity

- DD → syphilis, rubella and toxoplasmosis
- It occurs in babies to mothers who develop 1ry infection during pregnancy

2- <u>Perinatal and postnatal</u>

- Newborn acquire CMV at time of delivery due to contact to birth canal or through maternal milk
- <u>Clinically</u>
  - Asymptomatic
  - Hepatitis, rash, anemia, poor weight gain and pneumonitis

3- <u>CMV mononucleosis</u>

- Most common may follow transfusion of leucocyte containing blood product or occur spontaneously
- Affects all ages and sexually active adults
- <u>Clinically</u>
  - Prolonged fever, malaise, myalgia, fatigue and headache
  - Splenomegaly
  - Rash after ampicillin
  - Encephalitis (or any itis) but no pharyngitis or L.N
  - Hepatitis picture is similar to HAV, HBV with failure of drop of fever with appearance of icterus and jaundice lasts 2-3 weeks up to 3 months , it is a rare cause of post transfusion hepatitis

4- <u>CMV in immunocompromised patients</u>

- Very common 1- 4 months after organ transplantation
- The risk of the disease after 1ry infection is more than reactivation of dormant focus
- <u>Clinically</u>
  - Hepatitis: after liver transplantation
  - Pneumonitis: after lung transplantation
  - Pneumonia: in bone marrow transplanted patients (fatality is 88%)
  - Retinitis and disseminated disease in AIDS : prolonged fever, malaise, arthralgia, myalgia, respiratory involvement in the form of productive cough, tachypnea and hypoxia
  - GIT: ulcers from esophagus to the colon leading to perforation and bleeding
  - Meningoencephalitis
  - Extensive adrenal necrosis and in other organs

Diagnosis

1- **Isolation of the virus from urine or saliva**
   - Does not diagnose acute infection as the virus can be excreted for months to 1 year

2- **About ≥ 4 fold rise of antibodies by**
   - CFT
   - ELISA (IgM, IgG)
   - Immunofluroscence (IgM) مهم
   - Indirect haemagglutination
     - These titres can ↑ after 4 weeks from 1ry infection and remain high for years

3- **CMV specific IgM**
   - Diagnose acute infection, but false +ve results can occur in the presence of circulating Rh factor

4- CMV DNA by **PCR** in CSF diagnose CMV encephalitis

5- Detection of **CMV viraemia** is a predictor of acute infection

6- **Liver biopsy**
   - Non caseating granulomas
   - In immunosuppressed show characteristic intranuclear inclusions in the hepatocytes by immunoperoxidase and immunoflourscence technique

7- **Diagnosis of CMV mononucleosis**
   - Relative lymphocytosis with atypical monocytes
   - WBCs ↑, normal or ↓
   - Transaminases ↑
   - Alkaline phosphatase ↑
   - Cryoglobulin, Rh factor, cold agglutinins and ANA are +ve
   - Excretion of CMV in urine, genital secretion and saliva may persist for months or years

Treatment

1- **CMV immunoglobulin** → ↓ the rate of CMV associated syndrome and other associated infections

2- Prophylactic **acyclovir** → ↓ CMV infection, but not effective in active infection

3- **Gancyclovir** in immunosuppressed

- 5 mg /kg for 2 – 3 weeks
- It reduce retinitis and GIT damage
- Can eliminate CMV from blood, urine and respiratory secretions

4- **Foscarnet** (new drug)

- Na phosphonofermate
- Dose
  - 60 mg/kg/8 h **or** 90 mg/kg/12 h for 2 weeks
  - Maintenance dose: 90-120 mg/kg once daily
  - Given as infusion pump with proper hydration
  - There is dose adjustment for renal dysfunction or cardiomyopathy
- Indication
  - Used for resistant cases to gancyclovir (it inhibit viral DNA polymerase)
- Side effects
  - Genital ulcers
  - Renal dysfunction
  - Dysuria and nausea
  - ↓ Mg, K and Ca

5- **Cidofovir** [new drug]

Viral hemorrhagic fever

Etiology

Family	Virus/Syndrome	Geographic distribution	Mode of transmission	Human-human transmission	Antiviral treatment
Bunyaviridae	Congo-Crimean (CCHF)	Africa, **Middle east**, Asia & Europe (Crimea)	Contact with infected animals & by mosquito	Yes for CCHF, via body fluids. No for others.	Ribavirin for 10 days
	Rift Valley Fever	Africa, **Middle east**			
	Hantavirus (Hemorrhagic Renal Syndrome)	World-wide	Excreta of infected rats (inhalation with dust)		
	Hantavirus (Pulmonary Syndrome)				
Arenaviridae	Junin (Argentine HF)	South America	Excreta of infected rats (water contamination)	Yes for Lassa, via body fluids. Others are not usually.	Ribavirin for 10 days
	Machupo (Bolivian HF)	South America			
	Guanarito (Brazilian HF)	South America			
	Sabia (Venezuelan HF)	South America			
	Lassa fever	West Africa			
Filoviridae	Ebola HF	Africa	Exposure to tissues of African green monkey "Marburg"	Yes (body fluid transmission)	No antivirals
	Marburg HF				
Flaviridae	Yellow Fever	Africa, South America	Aedes egypi & africanus mosquito	No (blood is infective for 5 days in yellow fever)	No antivirals
	Dengue Fever				

Pathogenesis

1- Pathogenesis usually includes **combination of vascular damage, coagulopathy, immunological impairment and end-organ damage**, these lead to:

- Increased vascular permeability (the major pathophysiological process for most VHFs), allowing plasma to leak out the vessels causing edema, effusions & shock.

- Hemorrhagic manifestations which may be relatively minor (e.g. petechiae) or major (e.g. gastrointestinal bleeding as in Congo-Crimean hemorrhagic fever).
- Hepatic & renal failure.
- Encephalopathy.

Clinical presentation

1- **Incubation period**: 2-21 days, depending on agent.

2- **Onset:**

- Typically abrupt with filoviruses, flaviviruses, and Rift Valley fever.
- Insidious with arenaviruses.

3- **Initial symptoms:** prodromal symptoms lasting < 1 week

- High fever, headache, malaise, exhaustion.
- Muscle aches, joint pain.
- Non-bloody diarrhea.

4- **Clinical signs**

- Flushing, conjunctival injection (red eye).
- Pharyngitis (arenaviruses only).
- Rash, mucous membrane bleeding.
- Edema, hypotension, shock.

Diagnosis

1- **Clinical identification of suspected cases:**

- Temperature 101◦ F (38.3◦ C) for <3 weeks.
- Severe illness and no predisposing factors for hemorrhagic manifestations.
- Two or more of the following:
    - Hemorrhagic or purple rash.
    - Epistaxis.
    - Hematemesis.
    - Hemoptysis.
    - Blood in stool.

- Other hemorrhagic symptoms e.g. bleeding gum.
- No established alternative diagnosis.

2- Exposure criteria: One or more of the following exposures within the 3 weeks before onset of symptoms:

- Contact with blood or other body fluids of a patient with VHF.
- Residence in/or travel to a VHF endemic area.
- Work in a laboratory that handles VHF specimens.
- Work in a laboratory that handles bats, rodents, or primates from endemic areas.

3- Laboratory evidence

- Detection of viral antigens in blood by (ELISA) antigen detection.
- Detection of VHF viral antigens in tissues by immunohistochemistry.
- IgM and IgG ELISAs are also used.
- Viral isolation in cell culture for blood or tissue.
- Detection of viral genes using reverse transcriptase PCR (RT-PCR) from blood or tissues.

Treatment

1- Encourage **fluid intake with oral rehydration solution**.

2- Hypovolemic shock should be treated by **crystalloids and colloids**.

3- Fresh frozen plasma (blood transfusion usually not needed).

4- Ribavirin: started as soon as possible

- Indicated for: patients with suspected Lassa, Congo-Crimean, Rift valley fevers or hemorrhagic fever with renal syndrome.
- Dose: 30 mg/kg loading dose, then 16 mg/kg 4 times for 4 days, then 8 mg/kg 3 times for 6 days.

Arboviruses

Definition

1- Viruses transmitted between vertebrate hosts by **insects**, principally mosquitoes, ticks or sandflies

Clinical syndromes

1- Majority human infections with arboviruses are **asymptomatic** or cause a mild non-specific febrile illness

2- When an arbovirus causes disease, it usually leads to **one of three clinical syndromes**:

- Fever-arthralgia-rash (FAR).
- Viral hemorrhagic fever.
- CNS infection.

3- Most viruses cause a **single syndrome** but there can be **overlap** for example:

- Dengue viruses can present with FAR syndrome (Dengue fever), a hemorrhagic syndrome (Dengue hemorrhagic fever) and even CNS disease.
- West Nile virus is a cause of FAR syndrome with occasional CNS infection.

Fever-arthralgia-rash arboviruses

1- Chikungunya:

- Found in: Africa, Far East.
- Transmitted by: Aedes & Culex mosquito.

2- O'nyong nyong

- Found in: Africa.
- Transmitted by: Anopheles mosquito (the only one transmitted by Anopheles).

3- Ross River

- Found in: Australia.
- Transmitted by: Aedes & Culex mosquito.

4- **Colorado tick fever:** (easily confused with rickettsial disease & Rocky Mountain spotted fever)

- Found in: Rocky Mountain States (United States).
- Transmitted by: Tick.

5- **Dengue virus**

- Found in: Africa, South America.
- Transmitted by: Aedes **(egypi & africanus)** mosquito.

CNS arbovirus → arboviral encephalitis (see encephalitis)

Encephalitis

Infectious causes

Arboviruses (often epidemic)	1. Flaviviruses (Japanese encephalitis, West Nile virus, Murray Valley encephalitis). 2. Alphaviruses (Venezuelan, Eastern & Western equine encephalitis, Chikungunya). 3. Bunyaviruses (La crosse encephalitis).
Non-arboviruses (mostly sporadic)	1. Herpes viruses (Herpes simplex virus type 1 & 2, Varicella-Zoster, Epstein-Barr). 2. Enteroviruses (Coxsackie, echovirus, enterovirus type 71). 3. Paramyxoviruses (Measles, Mumps). 4. **Rabies**. 5. Human immunodeficiency virus.
Other infectious causes	1. Trypanosomiasis (especially Trypanosoma brucei rhodsiense). 2. Toxoplasmosis (occasionally presents with diffuse encephalitis). 3. Amoebic meningo-encephalitis (e.g. (Naegleria fowleri, Balamuthia mandrillaris). 4. Typhus (especially African tick typhus & scrub typhus). 5. Secondary syphilis & other spirochetes (e.g. relapsing fever).

N.B. acute disseminated encephalomyelitis occurs several weeks after an acute infection (often viral) or vaccination.

	Japanese encephalitis	**West Nile virus encephalitis**
Distribution	World-wide	Africa, Middle East, Asia
Transmitted by	Culex mosquito (breeds in rice fields).	Culex mosquitoe
Vaccination	Well-established inactivated vaccine	No vaccine

Clinical features

1- **Fever** & other non-specific symptoms (coryza, cough, headache) followed by disturbed level of **consciousness**.

2- **Focal neurological signs** (e.g. spastic rigidity).

3- **Signs of increased intracranial pressure** (e.g. vomiting).

4- Some patients may present with aseptic meningitis, febrile convulsions or polio-like acute flaccid paralysis.

Investigations

1- **CSF analysis** (lymphocytes < 500/mm^3, elevated proteins, normal glucose).

2- **ELISA** detection of IgM antibodies in serum or CSF.

3- Virus can be detected by **PCR** in CSF (the superior diagnostic test in most cases of viral encephalitis).

4- **CT or MRI** may show characteristic midbrain changes.

Treatment

1- **ICU** admission, mechanical ventilation.

2- **Acyclovir** is effective only for herpes simplex virus type 1 & 2.

3- **Treatment of complications:**

- Aspiration pneumonia → antibiotics.
- Seizures → diazepam, phenytoin or Phenobarbital.
- Increased intracranial pressure → osmotic diuretics e.g. mannitol.

Prevention

1- **Vaccination** (is only available for Japanese encephalitis).

2- **Vector control**

- Natural insecticides for mosquitoes.
- Intermittent irrigation of rice fields.

3- **Individual protection** by bed nets, protective clothing

Rabies

Mode of transmission

1- **Animal bite** (usually dog, less often wolf, fox, bat) with virus-containing saliva is the usual route.

2- **Salivary contamination** of abrasions or mucous membranes during rabid animal handling.

3- Occasionally, by **inhalation**.

Clinical features

1- **Incubation period:** 2-4 weeks, it's proportional to the distance the virus travel through peripheral nerve (shorter in children and after bites on neck or face).

2- **Initial symptoms:** usually include fever, insomnia, anxiety & other psychological disturbances.

3- **Encephalitic form:**

- Intermittent episodes of confusion, agitation and aggression with intervening periods of calm and lucidity.
- Copious saliva is characteristic (froth at the mouth).
- Painful spasm on throat muscles.
- Spasm often becomes more widespread involving the diaphragm & respiratory muscles.
- Death usually occurs within a week with respiratory and bulbar palsy.
- Some patients (20%), suffer paralytic rabies (i.e. ascending sensori-motor neuropathy).

Diagnosis is mainly clinical because

1- Laboratory tests for virus detection **aren't** available and currently lack sensitivity.

2- Diagnostic antibody tests **don't** become positive except after 8th day & are difficult to interpret in vaccinated patients.

Treatment

1- **Pre-exposure immunization:** active immunization

- Dose: 3 doses of cell culture vaccine or purified duck embryo vaccine given on days 0, 7 & 28.

- Indicated for:
    - Travelers to endemic areas.
    - High-risk groups (e.g. veterinarians & animal handlers).

N.B. the antibody response to vaccine may be impaired by concomitant Chloroquine administration, especially if intradermal route is used.

2- Post exposure first aid treatment

- Wash and flush the wound vigorously with water and soap or detergent.
- Application of ethanol 70% or aqueous solution of iodine.
- Topical application of rabies immunoglobulins **(RIG)** around the wound.
- Avoid suturing of wound; if suturing is necessary apply immunoglobulin locally.
- Apply antimicrobials and tetanus toxoid if necessary

3- Post-exposure immunization [passive and active]

Nature of exposure	Status of biting animal		Recommended treatment
	At time of exposure	During 10 days	
Contact but no lesion or indirect contact	Rabid		None
Licks of skin or abrasions or biting	Suspected as rabid	Healthy	Start vaccine, **but** stop it if animal remains healthy for 15 days.
	Suspected as rabid	Rabid	Active + passive
	Unavailable for observ.		Active + passive

- RIG should not be administered to previously vaccinated persons.
- All previously unvaccinated persons should be passively immunized with rabies immune globulin (RIG).
- If RIG is not immediately available, it should be administered no later than 7 days after the first vaccine dose.

- **Passive immunization**
    - Dose: 20 IU/kg for human RIG or 40 IU/kg for equine RIG.
    - Administration: ½ dose is infiltrated in & around the wound &½ dose is injected IM apart from 1st dose of vaccine
- **Active immunization**
    - WHO-recommended vaccines:

      © Human diploid cell vaccine (HDCV

      © Purified vero cell vaccine (PVCV)

      © Purified primary chick embryo cell vaccine (PCECV)

      © Purified duck embryo vaccine (PDEV)
    - WHO-recommended schedules:

1- Intramuscular administration (into deltoid, never buttock)

- Used for: all vaccines.
- Administration:
    - One dose of vaccine on days 0, 3, 7, 14 & 28.
    - Alternatively, two doses on day 0 (in each deltoid), one dose on days 7 & 21.

2- Two-site intradermal method

- Used for: all vaccines **except** HDCV.
- Administration: on days 0, 3, 7, 28 & 90.

3- Eight- site intradermal method

- Used for: HDCV & PCECV.
- Administration:
    - Day 0: 0.1 ml at each of eight sites (deltoids, supra-clavicular regions, lower quadrants of abdomen, and lateral aspects of thigh).
    - Day 28 & 90: 0.1 ml at deltoid.

Richettsiosis (Richettsial infections)

General features

Pathogenesis

1- **Causative organism**

- A group of diseases generally caused by species of **Rickettsia**, a genus of obligate intracellular gm –ve bacteria.

2- **Mode of transmission**

- They transmitted to humans by the bites, body fluids or faeces of various **arthropods**

3- The main features are **fever and rash**

4- Although they are widely distributed throughout the world, the species and associated human clinical diseases vary depending on the **geographical locations**

5- They multiply in capillary endothelial cells producing **lesions in** skin, CNS, heart, lung, liver, kidneys and skeletal muscles.

6- Endothelial proliferation associated with a perivascular reaction may cause **thrombosis & purpura**.

7- **An eschar** (a black necrotic crusted sore) is often found in tick & mite borne typhus due to vasculitis following immunological recognition of inoculated organisms.

8- **Regional lymph nodes** are often enlarged.

Classification

1- The **spotted fever group**, transmitted by ticks or mites

- I.P. → about 10-14 days

2- The **typhus group**, mainly transmitted by lice or fleas.

- I.P. → about 1 week

3- **Rickettsia related diseases** [Q fever]

Group	Organism	Disease	Vector	Reservoir
Typhus group	R. prowazekii	Epidemic “louse-born" typhus	Louse	Humans
	R. typhi	Endemic “flea-born" typhus	Flea	Rats
	Orienta tsugamushi	Scrub typhus	Mite	Rodents
Spotted fever group	R. rickettsii	Rocky mountain spotted fever	Tick	Rodents, dogs
	R. conorii	Mediterranean spotted "Boutonneuse" fever	Tick	Rodents, dogs
	R. africae	African tick-bite fever	Ixodes tick	Cattle
Rick. Related	R. like Coxiella burnetii.	Q. fever	Inhalation or ingestion	Cattle, sheep, goats

Lous borne typhus

Pathogenesis

1- Causative organism → Rickettsia prowazekii

2- Vector → pediculus humanus [human body louse]

3- Mode of infection → infected faeces of human body louse, usually by being scratched into the skin

4- The disease may be epidemic, and occurs esp. in malnourished migrant populations with poor hygiene e.g. in refugee camps

5- Distribution → common in Europe in the nineteenth century and was a frequent cause of death in concentration camps in 2nd world war

Clinical features

1- Incubation period → 12 days

2- High **fever**, myalgia, headache and prostration

3- The **conjunctiva** may be suffused and **delirium** is common

4- **The rash**

- Appears on the 3rd or 4th day
- Central and macular
- May later become petechial or purpuric

5- **Complications** → pneumonia and/or meningoencephalitis frequently occur later , sometimes, myocarditis

6- Untreated cases has **high mortality**

Diagnosis

1- Clinical, esp. in epidemic situations

2- Weil-Felix serological test → can still be useful

3- PCR is better

Treatment

1- Full supportive medical and nursing care

2- The disease usually respond well and rapidly to drug therapy

3- **Tetracycline**

- 500 mg /6 hr daily orally or I.V. for 1 week

4- **Chloramphenicol**

- 500 mg /6 hr daily orally or I.V. for 1 week

5- **Doxycycline**

- 200 mg/day for 7 days

6- Preventive measures esp. in epidemics

- Delousing procedures
- Doxycycline 200 mg given as a single dose to all at risk groups

Scrub typhus

Pathogenesis

1- Causative organism → Orientia tsutsugamushi (previously, R. orientalis or tsutsugamushi)

2- Vector → mites

3- Mode of infection → bites of infected larval mites

4- It is a zoonosis of rodents

5- Distribution → South East Asia, Oceania and northen Australia

Clinical features

1- Incubation period → 5-10 days

2- Small **eschar**, may be noted at the site of the mite bite

3- Abrupt **fever**, myalgia, headache and prostration

4- The **rash** as in louse borne typhus

5- **Delirium** is frequently marked

6- Generalized or localized **lymphadenopathy**

7- **HSM** may occur

8- **Pneumonia and myocarditis** may occur

9- Neuropsychiatric features are not prominent as in louse borne typhus and the overall **mortality is lower**

Diagnosis

1- Usually, clinical

2- The Weil-Felix test is insensitive

Treatment

1- **Doxycycline** [the most optimal treatment]

- 200 mg orally once daily for 3-7 days

2- **Tetracycline and chloramphenicol**

- Effective as in other forms of typhus
- Resistance has been reported

3- **Rifampicin or ciprofloxacin** → in resistant cases

4- **Preventive measures**

- Avoidance of mite-infested areas
- Impregnation of clothing with permethrin
- Prophylactic Doxycycline 200 mg weekly while in high risk areas

African tick typhus

Pathogenesis

1- **There are various forms of tick typhus**
   - Rocky Mountain spotted fever
   - Siberian tick typhus
   - Queensland tick typhus

2- **The causative organism**
   - Usually → R. conorii
   - In Zimbabwe → R. africae

3- **Vector** → various tick spp. (both reservoirs and vectors)

4- **Mode of infection** → bite of infected tick (the infection usually caught by travelers and campers in veld areas or grasslands)

Clinical features

1- **The illness mimic a mild attack of scrub typhus**

2- Usually noticeable **eschar with local lymphadenopathy**

3- **Mild fever** with toxaemia

4- The **central rash** may later spreads to the limbs

5- Complications are rare with **no mortality**

Diagnosis → usually clinical

Treatment

1- **Mild cases** → may not require treatment

2- **Tetracycline, chloramphenicol or doxycycline** → as in scrub typhus

3- **Azithromycin** → also effective

4- **Preventive measures**
   - Insect repellents
   - Appropriate clothing

Q fever

Causative organism → Rickettsia-like Coxiella burnetii

Mode of transmission

1- Cattle, sheep, goats are important reservoirs of the organism.

2- Inhalation of aerosols.

3- Ingestion of milk or milk products from infected animals is also reported.

Clinical features

1- <u>Acute Q fever</u>

- Fever, chills, sweats, severe headache and extreme fatigue.
- Conjunctival injection (red eye) is common.
- Nausea, vomiting, and diarrhea
- Dry cough & pleuritic pain develop in about 50% of patients.

2- <u>Chronic Q fever</u>

- Fever is usually absent or low grade. Patients may have nonspecific symptoms for up to 1 year before diagnosis.
- Endocarditis usually occurs in patients with previous valvular heart disease.
- Chronic renal insufficiency.
- Meningo-encephalitis.

Diagnosis

1- <u>Serology</u> is the most commonly used diagnostic tool. Indirect immunofluorescence is sensitive and specific and is the method of choice.

2- <u>Antibody detection</u> (IgG and IgM) against phase I & II antigens:

- IgG (titer > 1:200) and IgM (titer > 1:50) anti-phase II antigens indicate <u>acute disease</u>.
- IgG (titer > 1:800) and IgA (titer > 1:100) anti-phase I antigens indicate <u>chronic disease</u>.

3- <u>PCR</u> detects *C. burnetii* DNA in tissues.

Treatment [is not as effective as for rickettsial infections]

1- **Acute disease:**

- Doxycycline 100 mg twice/day for 2 weeks.
- Fluoroquinolones may also be helpful.

2- **Chronic disease (chronic endocarditis):**

- Doxycycline and hydroxychloroquine for 1.5 -4 years or for life.
- Alternatively, Rifampin (300 mg once daily) combined with doxycycline (100 mg twice daily) or ciprofloxacin (750 mg twice daily) has been used successfully.

Prevention

1- A whole-cell vaccine (Q-Vax) licensed in Australia effectively prevents Q fever in abattoir workers.

2- Before administration of the vaccine, skin testing with intradermal diluted *C. burnetii* vaccine is performed, serologic testing is undertaken, and a history of possible Q fever is sought.

3- Vaccine is given only to patients with no history of Q fever and negative results in serologic and skin tests.

N.B. Coxiella burnetti differs from rickettsia by:

1. It doesn't produce rash.
2. It's highly resistant to heat & disinfection.

SPIROCHEATAL DISEASES

Definition

1- The Spirochaetales include three genera pathogenic for humans and for other animals

- **Leptospira**, which causes human leptospirosis (Weil's sisease).
- **Borrelia**, which causes relapsing fever and Lyme disease.
- **Treponema**, which causes venereal syphilis.

Pathogenesis [Spirochetes share a common pathogenesis as follows]:

1- The spirochetes gain entry through **mucous membranes or abrasions** in intact skin.

2- They multiply locally in the skin (**causing skin lesion**), then the organism spreads to all organs.

3- Multiplication takes place in **blood (bacteremia) and in tissues**, and so the organism can be isolated from blood and cerebrospinal fluid (CSF).

4- Multiplication in **reticuloendothelial system** results in hepatosplenomegaly, they can damage the wall of small blood vessels; this damage leads to vasculitis with leakage and extravasation of cells, including hemorrhages.

5- They may **disseminate** to nervous system (meningo-encephalitis), heart (myocarditis), lung (cough) and kidney (renal failure).

6- After the start of antimicrobial treatment, a **Jarisch-Herxheimer reaction** may develop. This reaction is thought to be a response to lipoproteins released by dying spirochetes.

Leptospirosis

Etiology → Leptospira interrogans

Mode of transmission

1- Organisms gain entry to the human host through cuts, abrasions, and skin softened by prolonged water contact, contaminated by excreta of infected dogs, rodents.

Clinical features

1- Transient **skin rash** may be noted (macular, macula-papular or purpuric rash).

2- **Non-specific symptoms**: fever, headache, rigors.

3- **Musculoskeletal**: severe myalgia accompanied by marked tenderness of the calves, thighs and midback.

4- Conjunctival injection **(red eye)**, photophobia.

5- Other manifestations include **epistaxis**, sore throat and cough.

6- **CNS**: Neck stiffness

7- **Cardiovascular**: myocarditis

8- Abdominal pain and may be acute abdomen,

9- Diffuse lymphadenopathy, hepatosplenomegaly (**reticuloendothelial**).

Diagnosis

1- **Culture** (Fletcher's & Stuart's media): blood, cerebrospinal fluid, and urine.

2- Serology is most helpful, **agglutination test**

- A rise by of 4-folds or more is diagnostic.
- Titer >1:800 plus symptoms indicates active disease, 1:200 is suggestive.

3- **Antibody (IgM)** detection by ELISA is commercially available and has good sensitivity and specificity

Treatment

1- **Antibiotics:**

- Severe disease: IV penicillin G, ampicillin, or ceftriaxone.
- Mild disease: oral doxycycline or amoxicillin.

2- **Supportive treatment** for severe cases (fluids & ICU admission).

3- **For prophylaxis** in endemic areas, doxycycline (200 mg/day) has been shown to be effective.

Weil's disease (icteric leptospirosis)

1- It is a **severe form of leptospirosis** characterized by hemorrhage, jaundice, renal failure and pulmonary involvement.

2- It develops in **5–10%** of infected individuals.

3- It has mortality rates of **5–15%.**

4- **Treatment:**

- ICU admission.
- Antibiotics.

Lyme disease

Etiology → Borrelia burgdorferi

Mode of transmission → insect-borne disease transmitted by Ixodes tick (nymph not adult)

Clinical features

1- **Primary Lyme disease (early localized infection):**

- Skin rash: erythema migrans is the hallmark of disease
  - Macular expanding erythematous lesion with central clearing, commonly located in moist warm areas of the body (axilla, behind the knee or at belt line) where ticks prefer to feed
  - Begins one month after the tick bite
  - Painless, can cause itching

2- **Secondary Lyme disease (early disseminated disease):**

- Non-specific: Fever, headache, malaise.
- Conjunctival injection, photophobia **(red eye).**
- Musculoskeletal: Migratory joint, muscle, tendon and bone pains are common complaint.

- CNS involvement: neck stiffness, cranial nerve deficits (bilateral Bell's palsy is the commonest), peripheral neuritis.
- Cardiovascular involvement: conduction defects.

> The triad of meningitis, cranial nerve deficits and radiculonephritis is called **Bannworth's syndrome**.

3- **Tertiary Lyme disease (late disease):**

- Musculoskeletal manifestations are most common, but neurological involvement may occur.
    - Migrating arthralgia or frank arthritis causing joint swelling most commonly involves the knee & other large joints.
    - Joint aspiration may reveal presence of spirochetes (by PCR).
- Acrodermatitis chronica atrophicans, a chronic skin infection, containing spirochetes.

Diagnosis [mainly clinical]

1- **Clinically**: erythema migrans is pathognomonic for Lyme disease.

2- **Laboratory**: antibody (IgM & IgG) detection by ELISA.

- Not recommended in presence of erythema migrans.
- Detected in 60-70% of patients in early disease.
- Can be affected by antibiotic therapy.
- Negative results don't exclude the disease.

Treatment

1- **Antibiotics:**

- Early mild cases: doxycycline or amoxicilline for 21-28 days.
- Severe cases (i.e. meningitis of carditis): IV penicillin G or ceftriaxone for 14-30 days.
- Chronic arthritis: doxycycline for 30-60 days.

2- **Supportive treatment** for severe cases

Relapsing fever

Etiology

1- Louse-born relapsing fever (LBRF) → Borrelia recurrentis.

2- Tick-born relapsing fever (TBRF) → Borrelia duttoni.

Mode of transmission

1- Louse-born relapsing fever → body lice.

2- Tick-born relapsing fever → ticks.

Clinical features

1- Non-specific: fever, headache, malaise & mental confusion

- The febrile attack usually lasts 2-10 days ending by crisis manifested by subnormal temperature and profuse sweating.
- Apyrexial period lasts for 2-5 days.
- Number of relapses ranges from 2-8.
- Relapses occur more common in tick-born relapsing fever.

2- Skin rash: erythematous or petechial rash

3- CNS: meneingo-encephalitis.

4- Cardiovascular: myocarditis, arrhythmia.

5- Conjunctival injection, photophobia (**red eye**).

6- Jaundice, hepato-splenomegaly.

7- Musculoskeletal: tender calf muscles.

Diagnosis

1- Detection of Borrelia in:

- Fresh blood smears by dark-ground illumination.
- Thick blood smear stained by Giemsa stain.

2- Intraperitoneal inoculation of 1 cc of patient blood during pyrexia into mice, produces Borrelia in peripheral blood in 2-3 days.

3- Serology is unreliable.

Treatment

1- **Antibiotics:**
   - Effective antibiotics include: tetracycline, doxycycline, penicillin G, erythromycin & ciprofloxacin.
   - Ceftriaxone IV is recommended for patients with meningitis or encephalitis.
   - A single dose of antibiotic is effective in about 95% of cases of LBRF & about 80% of those with TBRF, however the usual practice is to give 5-10 days course to minimize the liklihood of relapses.

2- **Prophylaxis against (J-H reaction):**
   - Meptazinol: is an opioid antagonist given to reduce the severity of J-H reaction.
   - Antitumor necrosis factor alpha: is also effective in minimizing the J-H reaction.
   - Steroids are of **no** benefits in reducing J-H reaction.

Jarisch-Herxheimer (J-H) reaction

Definition

1- It's is a **systemic reaction** that follows initiation of antibiotic treatment in patients with spirochetal infection. It usually follows within a few hours of the first dose of antibiotic.

2- It occurs in **80-90%** of patients treated for LBRF and **30-40%** of those traeted for TBRF.

3- It's also reported in **70-90%** of patient treated for secondary syphilis & **10-25%** of those traeted for any stage of syphilis.

Clinical features

1- **Abrupt rise of fever**, chills, muscle aches, headache, reslessness & anxiety.

2- These symptoms are **often accompanied by** hyperventilation, tachycardia, flushing, and hypotension followed by collapse & shock.

Management

1- **Prophylactic** (see above).

2- Specific management: **antishock measures** (IV fluids, ICU admission).

N.B.

- Fever with red eye (conjunctival injection) increases the suspicion of spirochetal diseases.
- Tender calf muscles occurs in relapsing fever, leptospirosis

CHLAMYDIAL DISEASES

Causative organism

1- Chlamydias are non-motile **obligate intracellular parasites**, closely related to bacteria as they contain both DNA and RNA and have cell wall

2- They grow well in the **yolk sac** of embryonated eggs and are susceptible to tetracyclines and erythromycins

The main diseases are

1- Lymphogranuloma venereum (see STD).

2- Trachoma.

3- Non-specific urethritis.

4- Psiattacosis (Parrot fever).

Psiattacosis (Parrot fever)

Caused by: Chlamydia psittaci

Mode of transmission

1- C. psittaci is present in nasal secretions, excreta, tissues, and feathers of infected **birds** (parrots, pigeons, ducks, turkeys, chickens, and many other birds).

2- Psittacosis is almost always transmitted to humans by **inhaling** dusts from infected birds, cough droplets of infected patients and occasionally sexually.

Clinical features

1- I.P → 1-3 weeks

2- Fever, headache, chills and anorexia.

3- Dry cough which later becomes mucopurulent and chest pleuritic pain.

4- Pericarditis and myocarditis have been reported.

5- Condition usually lasts for about 1 month

Diagnosis

1- **Exposure to birds** (e.g. poultry workers) should increase suspicion.

2- Confirmation by **complement fixation test** showing high or rising antibody titer.

3- **X-ray** reveals pneumonitis

Treatment

1- **Doxycycline**: 100 mg twice/ day for 7-14 days.

2- **Erythromycin** may be used as an alternative in doxycycline-sensitive case or when doxycycline is contraindicated (e.g. children > 9 years or pregnancy).

Trachoma

The causative organism → Trachoma and inclusion conjunctivitis agent which is a strain of Chlamydia trachomatis

Clinical features

1- I.P. → about 1 week

2- The main symptoms are

- Bilateral conjunctival congestion
- Photophobia
- Lacrimation
- Eyelids edema

3- **Small follicles** develop in the conjunctivae or eyelids which gradually increase in size and number forming yellow grey semitransparent "Sagograin" granulations surrounded by inflammatory papillae

4- **Pannus formation** occurs with invasion of the upper half of the cornea by loops of vessels from the limbus

5- Involvement of the **cornea** usually reduces the vision

Diagnosis

1- Clinical picture

2- Conjunctival scrapings showing **cytoplasmic inclusion bodies** by Giemsa stain

Treatment

1- Tetracycline or erythromycin **eye ointment** applied twice or thrice daily

2- Oral doxycycline is helpful

Non-specific urethritis

Causative organism → Chlamydia trachomatis & ureaplasma urealyticum

Clinical features

1- I.P. → 1-4 weeks after sexual intercourse

2- Usually mild dysuria and mucopurulent discharge

3- Examination usually reveals red external urethral meatus with dried secretions

4- Pharyngitis and proctatitis may occur

5- In females → dysuria, vaginal discharge, pelvic pain and dyspareunia may be the presenting symptoms

Diagnosis

1- Clinical picture

2- Examination of **gram stained** urethral or vaginal secretions

Treatment: Doxycycline 100 mg twice/ day for 7-14 days.

Fungal infections

Histoplasmosis

Types

1- **Classical histoplasmosis**

- Causative agent → histoplasma capsulatum var capsulatum
- Distribution → mainly in central and south America

2- **African histoplasmosis**

- Causative agent → histoplasma capsulatum var duboisii
- Distribution → usually central and west Africa

Classical histoplasmosis

Etiology

1- **Mode of infection**

- Inhalation (the fungus is present in bat and bird excreta and is a particular hazard for cave explorers in endemic areas)

Clinical features

1- **Asymptomatic** → in many cases but may have serological evidence of past exposure

2- **Acute pulmonary histoplasmosis**

- Febrile bronchitic illness occurring 10-14 days after exposure
- Usually there is systemic malaise and myalgia
- Chest X-ray → shows generalized diffuse pulmonary shadows and sometimes hilar lymphadenopathy
- The illness may resolve spontaneously with no treatment

3- **Chronic pulmonary histoplasmosis**

- Sometimes the disease can cause asymptomatic single or multiple pulmonary nodules, often found on routine X-ray

- Usually there is focal consolidation and cavitation, often in the lung apices and this can mimic pulmonary TB (cough and hemoptysis may occur)

4- Acute disseminated histoplasmosis

- Invasion of RES (liver, spleen, bone marrow and LNs)
- Usually there is fever, weight loss, general weakness, lymphadenopathy and/or HSM
- This form often associated with AIDS

5- Chronic disseminated histoplasmosis

- Sometimes occur years after exposure
- Oral ulceration, hypoadrenalism, meningitis and endocarditis can occur

6- Atypical presentations

- Polyarthritis or polyarthralgia, erythema muliforme, erythema nodosum and hypoadrenalism

Diagnosis

1- Tissue biopsy

- The fungus present in body secretions or tissues e.g.
  - Sputum
  - Buffy coat layer
  - Lymph node aspirates
  - Bone marrow samples
  - Biopsies of liver and pulmonary nodules

2- Culture → if available, the yeast can be grown from sputum or blood

3- Serological tests

4- Intradermal histoplasmin skin test

Treatment

1- Treatment should be **reserved for** severe vases or immunocompromised patients

2- Drugs

- Itraconazole 200-400 mg/day
- Fluconazole also effective

- Amphotericin B is more difficult and toxic to use but it is widely available

3- **In AIDS patients**, relapses are inevitable and if possible, patients should receive long term itraconazole or fluconazole as 2ry prophylaxis

Manifestation	Primary therapy	Duration
Acute pulmonary disease	Treatment likely not indicated If symptoms persist > 1 mo or severe pneumonia with hypoxia, treat with itraconazole 200 mg tid for 3 days followed by bid. Lipid amphotericin B 3-5 mg/kg/d is alternative in severe cases	6-12 wk
Acute dissemination; severe disease; immunocompromised	Lipid amphotericin B 3-5 mg/kg/d i.v. for 2 wk or until clinically improved, then itraconazole 200 mg PO bid	12 mo followed by long term suppression for immunosuppressed; if HIV/AIDS until CD4 count > 200 for 6 mo
CNS histoplasmosis	Lipid amphotericin B 5 mg/kg/d for 4-6 wk followed by itraconazole 200 mg PO 2-3 x daily	Minimum 6 mo followed by lifelong suppression in immnuocompromised
Chronic or cavity pulmonary histoplasmosis	Itraconazole 200 mg PO once or twice daily	Minimum 12 mo
Mediastinal fibrosis	Antifungall therapy likely of no benefit	----------
N.B. goal serum itraconazole level → > 1 µg/mL		

African histoplasmosis

Clinical features

1- **Skin nodules or ulcers**

2- Enlarged lymph nodes or lytic lesions in bones

3- Disseminated disease can occur with lung and GI involvement

Diagnosis → histologically from biopsy specimens

Treatment

1- As classical histoplasmosis

2- Association with HIV is much less certain than with acute disseminated histoplasmosis caused by H.capsulatum var capsulatum

Candidiasis

Etiology

1- **Candida albicans** is the most common pathogen

2- **Other species** include: candida tropicalis, candida krusei and candida dubliniensis

3- Infection by candida glabrata and candida parapsilosis tend to occur in patients with prior antigungal exposure

4- **Candida albicanus**

- Gram +ve oval budding yeasts which produce pseudohyphae
- It is part of the normal flora of mm of the upper respiratory, GI and female genital tract → superinfection

Risk factors

1- HIV (esp. if CD4 count < 200 cell/mm^3)

2- DM

3- Prolonged corticosteroids and antibiotic therapy

4- Chronic debilitating diseases

5- Indwelling urinary catheters

6- IV drug abuse

Types and clinical features

1- **Oropharyngeal candidiasis**

- Burning pain in the mouth and altered taste sensation
- Thrush is a removable white creamy plaque on any oral mucosal surfaces
- These plaques have an erythematous base when scraped

2- **Esophageal candidiasis**

- This is an AIDS defining condition
- Dysphagia or odynophagia ± oropharyngeal lesions
- Diagnosis made by endoscopy → see GIT

3- Vulvovaginal candidiasis

- Itching, vaginal erythema with white discharge
- Dysuria, dyspareunia and erythema of the labia and vulva
- The condition is favoured by high pH, DM or prolonged antibiotic use

4- Skin infection

- Skin invasion occurs in warm moist areas which become red and weeping such as the axilla, intergluteal folds or inframammary folds most common in obese and diabetics

5- Nail infection

- Involved when repeatedly immersed in water as in persons involved in dish washing
- Painful redness and swelling of nail folds, thickening and loss of nail i.e. paronychia

6- Disseminating candidiasis & chronic mucocutaneous candidiasis

- Candidiasis may disseminate to many organs or cause chronic MC candidiasis esp. in debilitated children, diabetics, immunosuppressed patients or drug addicts
- It is usually associated with T cell deficiency

Diagnosis

1- Clinical

2- Direct microscopic examination

- Smear or exudates from the lesions shows large oval gram +ve budding yeast cells with pseudohyphae

3- Culture

- Done on nutrient agar, corn meal agar and SDA
- Colonies are soft, cream coloured with a yeasty odour
- Identified by
    - Morphology (all candida)
    - Germ tube formation in serum (C.albicans)
    - Chlamydospore formation on corn meal agar (C.albicans)

- C.albicans ferments glucose and maltose with acid and gas production

4- **Upper endoscopy** → for esophageal candidiasis

Treatment

1- **Oropharyngeal candidiasis**

- Topical antifungal therapy
  - Clotrimazole oral troches (10 mg 5 times daily)
  - Nystatin oral susp. (500,000 u/5 mL 4 times daily)
- Oral azoles
  - Indicated in patients with moderate to severe disease, recurrent infections and advanced immunosuppression (CD4 < 100 cells/mm^3)
  - Fluconazole 200 mg loading dose followed by 100 to 200 mg once daily for 7-14 days after clinical improvement

2- **Esophageal candidiasis**

- Fluconazole 400 mg loading dose followed by 200 to 400 mg PO or i.v. once daily
- Those refractory to fluconazole after 1 week may be switched to
  - Voriconazole or posaconazole (oral therapy) or echinocandins e.g. caspofungin if i.v. is required
  - Amphotericin B is an alternative option
- Pregnant patients
  - Should be treated with amphotericin B since azoles are teratogenic

3- **Vulvovaginal candidiasis**

- Topical antifungal therapy
  - Clotrimazole, miconazole, butoconazole or tioconazole cream

- Oral fluconazole
    - 150 mg as a single dose is effective
- Complicated cases
    - May require prolonged therapy either with topical treatment > 7 days or 2 doses of fluconazole 150 mg given 72 hours apart

4- Skin lesions → nystatin or clotrimazole ointments

5- Mucocutaneous candidiasis → ketoconazole

6- Disseminated candidiasis → amphotericin B I.V. + ketoconazole

PROTOZOAL DISEASES

Habitat	Protozon
Intestinal protozoa	- Entamoeba histolytica - Giardia lamblia - Balantidium coli - Cryptosporidium parvus - Isospora belli - Cyclospora caetanensis
Urogenital protozoa	-Trichomonas vaginalis
Blood protozoa	-Plasmodium - Babesia
Blood and tissue protozoa	- Leishmania - Trypanosoma - Toxoplasma gondii - Potentially pathogenic free living amoebae * Naegleria fowleri * Acanthamoeba species
Lung protozoa	- Pneumocystis carinii
Different systems of the body	- Microsporidia

MALARIA

Species

1- **Plasmodium falciparum:**
   - It causes malignant "sub-tertian" malaria.
   - Periodicity occur over 24 hrs i.e. every day
   - It's very rare in Egypt

2- **Plasmodium vivax:**
   - It causes tertian malaria
   - Periodicity occurs over 48 hrs i.e. every 3rd day

3- **Plasmodium ovale:**
   - It causes tertian malaria
   - Periodicity occurs over 48 hrs i.e. every 3rd day

4- **Plasmodium malariae:**
   - It causes quartan malaria.
   - Periodicity occurs over 72 hrs i.e. every 4th day

Pathogenesis

1- Source
   - Human patients
   - Reservoir host → chimpanzee in some parts of Africa (P. malariae)

2- Infective stage → sporozoites

3- Definitive host → Anopheles mosquito

4- I.H → man

5- Mode of transmission
   - Bite of the night-biting female anopheles mosquito (Anopheles pharaonesis & sergenti) → relapse
   - Blood transfusion from an infected donor or in drug addicts
   - Transplacental
     - Any other route of transmission than the natural route (by mosquito) will not lead to chronic malaria or relapse as there will

be no liver stages (no exo-erythrocytic schizogony). Only clinical attacks occur that is treated by schizonticidal drugs

6- Distribution

- Areas with significant numbers of malaria cases include Africa, the Middle East, India, South-east Asia, South & Central America and parts of the Caribbean
- *P. falciparum* predominates in Africa, New Guinea, and Haiti
- Malaria is found in lower rather than upper Egypt

Clinical features

1- The clinical manifestations of malaria are nonspecific. If the **exposure history** is not appreciated, the infection can be mistaken for other febrile illnesses

2- **Incubation period:**

- 9 - 40 days
- May be prolonged in cases of non-falciparum malaria (6 - 12 months in *P. vivax*, and years for *P. malariae* and *P. ovale*).

3- There are no recognized symptoms associated with liver phase of malaria or rupture of tissue schizont. Development of blood phase is necessary for malarial illness as red cell rupture is associated with release of malaria toxins

4- Prodromal symptoms which are **flu-like**.

5- **Febrile paroxysms** i.e. clinical attacks which coincide with rupture of red cells and release of parasite toxins: (often recognized in P.vivax)

- **Stages:** malaria paroxysm consists of:
  - Cold stage: The patient complains of sudden shills (shivering or rigors) and extreme cold because his temperature rises sharply (lasts 10 -15 minutes)
  - Hot stage: the patient suffers high fever sustained for a few hrs, hot-dry-flushed skin and rapid full pulse (lasts 2 – 6 hours), may be complicated by hyperpyrexia

- Sweating stage: there is profuse sweating (even drenched). The temperature falls rapidly and the patient is weak and exhausted. (Lasts several hours).

- **Patterns:** malaria paroxysms are repeated as follows:
  - Every 48 hours in P. ovale and P. vivax hence, its name tertian malaria
  - Every 72 hours in P. malariae hence, its name quartan malaria
  - Every 36 – 48 hours or irregularly in P. falciparum
- **Important consideration**
  - History of recent febrile symptoms and/or repeated temp. measurement are important as some patients may be afebrile at one particular time
  - Rarely, patients may be persistently afebrile in severe P. falciparum infection

6- Anemia: (due to hemolysis and B.M suppression)

- Merozoites of P. vivax and P. ovale invade only reticulocytes
- Merozoites of P. malariae invade only old RBCs at end of their life
- Merozoites of P. falciparum invade all stages of RBCs → **severe hemolysis**

7- Splenomegaly or hepatosplenomegaly:

- In all types due to enhanced phagocytosis of RBCs remnants and other debris of schizogony
- In repeated attacks → hyperactive malarial splenomegaly ®

8- Jaundice:

- Mild caused by hemolysis occur in all types (unconjugated)
- Severe jaundice unusual, but can occur in P. falciparum (combination of hemolysis + impaired liver function)

9- Severe falciparum malaria → ®

10- Immune disorders in malaria → ®

11- Malaria in pregnancy → ®

Severe falciparum malaria

1- **P. falciparum** infection is usually severe and fatal due to clumping of parasitized red cells and adherence to specific receptors on endothelial wall of capillaries of internal organs → occlusion, anoxia and necrosis

2- Clinical picture of falciparum malaria takes **different forms** according to site of occlusion

3- **Altered consciousness and coma**

- Several causes must be considered before diagnosis of cerebral malaria
    - Metabolic disturbances such as hypoglycemia or acidosis → correction may restore consciousness
    - Seizures that sometimes manifest by only very minor twitching movements → anticonvulsants may restore consciousness
    - Postictal state → recovery within a few minutes or hrs
    - Very severe anemia may impair consciousness
- If non of these complications accounts for the coma or if coma persists despite correcting these complications → cerebral malaria is diagnosed
- It is important not to overlook other possible explanations of the illness (e.g. meningitis, encephalitis, severe pneumonia or head trauma) in an individual who happens to be parasitaemic

4- **Cerebral malaria:**

- **Definition:**
    - Diffuse disturbance of cerebral functions, characterized by altered consciousness and commonly accompanied by convulsions.
    - Strict definition requires that the parasitaemic patient be unable to localize a painful stimulus (GCS $\leq$ 8; BCS $\leq$ 2), that coma persists despite correction of metabolic defects and seizures and that no other explanation for the coma can be found
- **Pathogenesis:** remains unclear but may be due to
    - Presence of large number of erythrocytes containing mature parasites in the capillaries & venules consuming essential

nutrients such as glucose & releasing toxic products such as lactate

- Substances released form rupture of red cells induces release of cytokines form host cells in excessive local & systemic concentrations
- Increased intracranial pressure, cerebral edema & to lesser extent the mass of sequestrated parasitized RBCs

- **Manifestations:**
  - The onset may be gradual or sudden within hours or days of the first febrile symptoms of malaria.
  - Coma is preceded by fever & may be accompanied by flaccidity of limbs or hypertonicity and opisthotonos.
  - May be coma without any preceding fever or other symptoms (not uncommon in children).
  - Any repetitive muscular movement may reflect underlying seizure activity
  - Recently characteristic retinopathy has been observed in children & adults with cerebral malaria (distinctive of malaria- direct ophthalmoscope).
    - Areas of retinal whitening (focal areas of retinal ischemia), best seen immediately around the fovea (but always sparing the fovea itself)
    - Orange or white discoloration of retinal vessels and capillaries in scattered parts of the retina
  - Most children with cerebral malaria have white-centred retinal haemorrhages (not distinctive of malaria)
  - About 10% of children have some degree of papilloedema (not distinctive of malaria)
- **Treatment and outcome:**
  - Specific and Supportive treatment of malaria → about 80% recover within 1-3 days after the start of treatment

- After recovery → 5-25% of patients are left with neurological deficit such as hemiparesis, cerebellar ataxia, amnesia, diffuse spasticity or epilepsy

5- <u>Black water fever:</u>

- **Definition:**
  - Massive intravascular hemolysis associated with hemoglobinuria & renal failure
  - It occurs in non-immune adults with severe plasmodium falciparum infection.
  - In children in the endemic areas, hemoglobinuria sometimes occurs in P.falciparum but rarely accompanied by renal failure.
- **Pathogenesis of massive hemolysis:**
  - High level of parasitaemia (> 100,000 organism/cm)
  - Hemolysis of infected and non infected RBCs
  - Insufficient and irregular treatment with quinine → which renders the parasitized RBCs antigenic and autoimmune reaction occur against these RBCs
  - Hemolysis may be precipitated by a drug or dietary factors in an individual with G6PD deficiency → hemolysis in this condition usually only affects the older cells, so ceases when the hemoglobin has dropped to about 6 g/dl
- **Clinically**
  - Fever, rigors and vomiting
  - Severe anemia + jaundice
  - Dark red or black urine [port wine]
  - Shock
  - Oliguria or even anuria (due to acute tubular necrosis resulting from renal ischemia due to severe intravascular hemolysis)
  - The parasites rapidly disappear from the blood during the attack or become very scanty

- **Prognosis** → either recovery or fatal termination due to heart failure, acute renal failure or hyperpyrexia with coma and delirium
- **Treatment:**
    - Bed rest, replacement of fluids, packed RBCs transfusion
    - Corticosteroids → parenterally and orally is life saving
    - Renal dialysis if needed
    - Specific antimalarials → (avoid quinine) only limited therapy is needed as most of the parasites are destroyed by hemolysis, but prophylactic treatment should be continued after the attack

6- <u>Dysenteric malaria:</u>

- Abdominal pain and vomiting due to ischemic changes of GI wall
- GI bleeding due to ischemic changes in capillary bed of gut wall
- Loose stools with blood

7- <u>Choleric malaria</u> → with watery diarrhea

8- <u>Pulmonary oedema:</u>

- Due to DIC and anoxia affecting pulmonary microcirculation

9- <u>Algid malaria:</u>

- As a result of pulmonary oedema, GI bleeding or Gm –ve septicemia, severe hypotension rapidly develops with impaired vascular perfusion, vascular collapse and shock

10- <u>Hypoglycemia:</u>

- Is a common complication of severe malaria esp. in children and pregnant women and is associated with a poor prognosis
- Causes
    - Cytokine-induced impairment of hepatic gluconeogenesis
    - Increased consumption of glucose by the malaria parasites
    - As a complication of quinine or quinidine therapy → stimulate the pancreas to secrete insulin

11- Renal failure:

- The pathogenesis is unclear but may be related to RBC sequestration interfering with renal microcirculatory flow and metabolism

12- Severe anemia

- Commonly seen in children between 6-24 months of age infected with P. falciparum
- Leads to breathlessness, weakness and occasionally, impaired consciousness
- Dyspnea in a child with severe malaria anemia → is most commonly a manifestation of acidosis; occasionally, dyspnea is a result of heart failure

13- Acidosis

- Tissue anoxia leads to anaerobic metabolism, release of lactic acid & other acids
- Rapid fluid volume replacement may be life-saving

14- Bleeding disorder

- Minor degree of DIC enough to cause bleeding occasionally in adults

Microcirculatory arrest in P. falciparum infection

Organs most affected	Main symptoms or signs	Typical misdiagnosis
Stomach and intestines	Vomiting and diarrhea	Gastric flu; cholera (diarrhea is not bloody)
Brain	Delirium, disorientation, stupor, coma, convulsions, focal neurological signs	Encephalitis, meningoencephalitis (there may be misleading CSF abnormalities)
Kidneys	Renal failure ± oliguria or haemoglobinuria	Nephritis
Liver	Jaundice and fever	Hepatitis
Lungs	Pulmonary edema	Pneumonia, heart failure

Malaria in pregnancy

1- All types → **abortion**

2- **Anemia** is common → esp. with P.falciparum

3- **Low birth weight** → esp. in 1st pregnancy babies in P.falciparum endemic areas (the placenta becomes packed with both late stage parasites and host mononuclear cells)

4- **Congenital infection**

- More common with P. vivax
- Presents within a few days or weeks of birth
- Clinically → fever + hemolytic anemia + failure to thrive

5- In endemic areas, it is common to find malaria parasites in **umbilical** venous blood → usually disappear within the first 2 days

Immune disorders in malaria

1- **Malarial nephrosis and intractable nephritic syndrome**

- Occasional with P. malariae
- Cause → antigen antibody complex
- Poor prognosis even with treatment

2- **Hyper-reactive malarial splenomegaly** → ®

3- Acute attack of malaria has general **immunosuppressive effects**

- May accounts for the tendency of the EBV to produce Burkitt's lymphoma in malaria endemic areas

Diagnosis

1- **Direct:**

- **Thin blood films:** [Giemsa or Leishman stains]
  - Show the undistorted parasite within RBCs.
  - It's of most use for detailed parasite morphology & species identification
  - In P.falciparum → only 2 stages are present in peripheral blood (ring stage and gametocytes) → because RBCs with late

trophozoites and schizontes adhere together and stick to intima of capillaries, so not seen in blood films

- Disadvantage: low sensitivity (requires a very prolonged search to detect low parasitaemia)

- **Thick blood films:** [Giemsa or Leishman stains]
  - Allows for more RBCs to be examined i.e. more sensitive than thin films [answer the question 'does the patient have malaria']
  - Disadvantage: different species can't be distinguished

2- Serology:

- IFAT is the most frequently used.
- Mainly used for excluding malaria in patients with recurrent bouts of fever who does not present during a bout or in surveys.
- Of no use for acute attacks
- Incapable of distinguishing different species

3- New methods:

- Rapid dipstick-like tests:
  - They detect parasite enzymes or antigen in whole blood sample.
  - They have the advantage of not requiring a microscopy.
  - Most are sensitive & specific for P. falciparum.
- Quantitative buffy coat (QBC) technique:
  - It depends on the fact that parasitized red cells have specific gravity higher than non-parasitized cells.
- PCR reaction test → detect parasite DNA

4- However the above-mentioned new methods of malarial diagnosis are useful in research studies, they haven't replaced thick & thin films for routine clinical diagnosis.

5- Always consider malaria in the traveler from a developing country who presents with:

- Influenza-like syndrome. Or
- Attacks of fever. Or

- Jaundice. Or
- Confusion or coma.

Supportive treatment

1- Antipyretics:

- Oral or rectal paracetamol is the drug of choice.
- Tepid sponging and fanning also offers temporary benefits.

2- Rehydration (I.V. fluids):

- When vomiting and diarrhea are prominent.
- In patient with deep breathing suggesting acidosis

3- Anticonvulsants:

- Rectal diazepam or lorazepam (drugs of choice).
- Alternatives are paraldehyde (rectal or IM) or Phenobarbital (IM).

4- Blood transfusion:

- Indications
  - When Hb concentration is < 4 gm/dl (hematocrit < 12 %) OR
  - When higher Hb levels are accompanied by coma, acidosis or hyperparasitemia
- In most cases → Hb conc. ↑ rapidly when the attack terminated by specific chemotherapy

5- Management of DIC:

- Fresh whole blood, fresh-frozen plasma or platelet-rich plasma.

6- Management of renal impairment:

- If oliguria persists → maintenance of careful fluid balance.
- Peritoneal dialysis of hemodialysis may be life-saving

7- Management of hypoglycemia:

- 10 – 40 ml of 50% dextrose diluted x 3 with saline and infused over 5 – 10 minutes

8- Management of acidemia:

- Rehydration, blood transfusion and antimalarial therapy are usually sufficient.
- Bicarbonate infusion may be attempted in severe acidosis.

9- **Antibiotics indications**

- If the diagnosis of malaria is in doubt
- In an unconscious patient in whom lumbar puncture is deferred
- In patient groups known to have a high risk of bacteremia accompanying severe malaria e.g. children with cerebral malaria or severe anemia

Specific treatment

Chemoprophylaxis

1- **Concepts:**

- It involves regular administration of drugs to prevent clinical symptoms.
- It's routinely advised only for non-immune travelers visiting endemic areas.
- No prophylactic regimen can be completely suppress P. falciparum malaria esp. in non-immune people

2- **Drugs taken for prophylaxis, act in two ways:**

- Schizonticides: they kill the parasites that enter red cells.
- Causal prophylactics: prevent development of pre-erythrocytic schizonts in liver and may have blood schizonticidal effects

3- **Prophylaxis should start** 2 weeks before traveling to insure that no intolerable side effects develop and continue for 4 weeks after return.

4- **Drugs of prophylaxis in Chloroquine-sensitive areas:**

- Oral chloroquine 300 mg/week (drug of choice).

5- **Drugs of prophylaxis in Chloroquine-resistant areas:**

- Oral chloroquine 300 mg/week combined with proguanil 100 mg/day Or,
- Oral mefloquine 250 mg/week (3.5 mg / kg / week) Or,
- Oral doxycycline 100 mg / day Or,
- Oral primaquine 0.5 mg / kg / day Or,
- Oral atovaquone 250 mg combined with proguanil 100 mg / day (in a combination tablet called Malarone).

6- Mefloquine

- Structure → 4-quinoline methanol drug related to quinine
- Side effects
  - Headache, dizziness and disturbance of sleep
  - Fits, psychomotor disturbances and psychoses
- Contraindications
  - History of convulsions or neuropsychiatric disease
  - Patients on cardiosuppressant drugs or beta-blockers
  - Pregnancy not a contraindication
- Uses
  - Prophylaxis in Chloroquine-resistant areas
  - May be used in acute attack as a single oral dose of 750-1250 mg

7- Proguanil

- Structure → synthetic biguanide
- Action
  - Slowly acting schizonticidal
  - Causal prophylactic
- When used as a prophylactic → should be combined with another drug
- Side effects [the safest antimalarials]
  - Epigastric pain or heart burn
  - Mouth ulcers
  - Gross hematuria with overdose
  - Safe in pregnancy, but folic acid should be given

8- Atovaquone –proguanil → only needs to be continued for a week after leaving the malarious area (causal prophylactic)

9- Doxycycline

- Useful in the areas of South East Asia, where there is resistance to both chloroquine and mefloquine
- CI → in pregnany, lactation and < 9yr
- An occasional toxic effect is a rash caused by photosensitization

Treatment of clinical attack in chloroquine-sensitive areas

1- Chloroquine:

- Structure → synthetic compound of the 4-aminoquinoline group
- Mode of action:
    - It's a powerful schizonticide.
    - It also has anti-inflammatory effect, so helps to reduce non-specific symptoms of malaria (malaise, myalgia, headache).
- Dose:
    - Oral → 600 mg followed by 300 mg after 6 hrs, then 300 mg/day for 2 days (total of 1.5 gm).
    - IV → 5 mg/kg (maximum 300 mg) infused over 3 hrs in saline, repeated every 8 hrs to total of 25 mg/kg.
    - IM or SC → 2.5 mg/kg (maximum 150 mg), repeated every 4 hrs to total of 25 mg/kg.
    - Change to oral treatment as soon as the patient can take it
- Side effects:
    - GIT upset (nausea, vomiting).
    - Hypotension
    - Itching (in black persons)
    - Chronic usage may cause visual disturbances or cause the hair to turn white

Treatment of clinical attack in chloroquine resistant areas

(treatment of drug resistant malaria)

1- Artemisinin drugs:

- Definition and effect:
    - They are compounds derived from plants Artemisia annua, which has been used for years in treatment of fever in China.
    - The plant's active components (arte-ether, arte-mether, artesunate) are highly effective antimalarials, active against chloroquine-resistant & multidrug-resistant P. falciparum and useful in

treatment of severe & complicated malaria as well as uncomplicated malaria.

- Parasites are cleared from circulation faster by artemisinins than by quinine or chloroquine.
- In the treatment of severe disease, artemisinins are less toxic & more convenient than quinine.

- Mode of action:
  - They rapidly kill the asexual blood stage of parasites (sporozoites) so a second antimalarial drug is needed to kill the remaining parasites.
  - They reduce gametocyte production which in turn reduces transmission of malaria locally.
  - They have short half-lives so they are used in combination with other antimalarial drugs as follows:

© Co-artem (artemether-lumefantrine):

→ It is the 1st line therapy for uncomplicated malaria.

→ Absorption of lumefantrine is increased considerably by fat, therefore the drug should be taken with food.

© Amodiaquine-artesunate:

→ Amodiaquine has a molecule similar to chloroquine, given in the same dose (600 mg followed by 300 mg after 6 hrs, then 300 mg for 2 days) and has the same side effects as chloroquine.

- Dose:
  - Standard adult dose of co-artem is 4 tab. Twice /day for 3 days
  - WHO-approved adult dose of co-artem (artemether-lumefantrine) is 4 tablets at 0, 8, 24, 36, 48 and 60 hours (six doses).
  - If artemisinin drugs used alone for treatment of P.falciparum → must be given for at least 5 days and preferably 7 days (shorter doses followed by recrudescence in 50% of cases)
- Available forms:
  - Artemether is an oil-soluble derivative, suitable for IM injection.

- Artesunate is available as tablets, suppositories & powder for preparing IV solution.

- Indications:
  - Uncomplicated and severe malaria.
  - Drug resistant malaria.
  - Anti-helminthic i.e. a broad spectrum of activity against a wide range of trematodes, including Schistosoma japonicum, S. mansoni, S. haematobium, Clonorchis sinensis, Fasciola hepatica, and Opisthorchis viverrini.
  - Cancer treatment i.e. Chinese scientists have shown artemisinin has significant anticancer effects against human hepatoma cells
- Side effects:
  - GIT upset e.g. nausea, vomiting, anorexia and dizziness
  - Mild blood abnormalities have been noted
  - Rarely allergic reactions.

2- Fandisar (sulfadoxine-pyrimethamine):

- The two-component drugs inhibit different enzymes required for folic acid synthesis by the parasite.
- It has been widely used as first-line treatment for malaria in many countries due to the highly convenient, inexpensive single-dose therapy but increasing resistance has greatly reduced its usefulness in recent years.

3- Malarone (atovaquone-proguanil):

- A recently licensed combination for treatment of uncomplicated P. falciparum malaria.
- The standard regimen is 4 tablets for 3 days. Not used in national programs as it's expensive.

4- Quinine

- Structure → natural alkaloid derived from cinchona bark
- Action

- Powerful schizonticidal
- Has anti-inflammatory action

- Indications
  - Severe P. falciparum malaria
- Dose
  - Oral → 600 mg /8 hrs for 7-10 days
  - I.V infusion → load dose of 20 mg/kg (max. 1400mg) quinine HCL over 4 hr in isotonic glucose-electrolyte fluid (e.g. 1/2 strength Darrow's -5% dextrose) → then doses of 10 mg/kg are similarly infused over 4 hr at 8 hr intervals for adults or infused over 2 h at 12 hr intervals for children → change to oral as soon as possible
  - I.M. → as with i.v , the loading dose 20 mg/kg; to reduce the volume of this large dose, it may be divided between the 2 thighs and further divided by given 1/2 at time zero and the remainder 4 h later
- Side effects
  - Cinchonism → inevitable with normal doses but not necessitate stoppage of treatment (tinnitus, deafness, dizziness, nausea and vomiting)
  - Hypoglycemia, hypotension , thrombocytopenia or erythematous rash
  - Over dose → deafness, blindness, severe hypotension, abortion

Radical treatment

1- After treatment of clinical attack to **kill hypnozoites** of *P. vivax* and *P. ovale* to prevent relapse [NOT for blood transfusion infection or falciparum]

2- **Primaquine [8-aminoquinoline]**

- 30 mg base / day for 10-14 days → in *P. vivax* (the dose may doubled in some strains-resistance-)
- 15 mg base / day for 10-14 days → in *P. ovale*

- OR 45 mg base / week for 6 weeks (in G6PD deficiency, usually well tolerated)

Classifying antimalarial drug resistance

1- Early treatment failure

- Severe illness with parasitaemia during the 1st 4 days after treatment or
- Persistence of fever and parasitaemia throughout those 4 days

2- Late treatment failure

- Clinical improvement but fever and parasitaemia recur by day 14

3- Adequate clinical response

- The patient may have either fever or parasitaemia by day 28 but not both + There was neither early nor late treatment failure

4- Adequate clinical and parasitological response

- The patient has no parasitaemia by day 28 +
- There was neither early nor late treatment failure

Oral question → difference between relapse and recrudescence

* Relapse → re invasion of RBCs by merozoites released from the liver (P. vivax and ovale)
* Recrudescence → the patient has persistent low grade parasitaemia, and when the immunity ↓ → the erythrocytic parasites increase enough to produce clinical attack

Hyper-reactive malarial splenomegaly

1- Etiology

- Caused by an abnormal response to repeated malarial infections that results in overproduction of immunoglobulin M
- The consequent immune complexes are removed by the spleen which can enlarge to huge proportions

2- Age → 20-40 y

3- Sex → more common in women

4- Clinical and laboratory features

- Asymptomatic initially
- Eventually develop anemia, malaise and abdominal discomfort
- Sudden episodes of life threatening hemolysis in pregnant womens may occur
- Hepatomegaly
- Hypersplenism causes thrombocytopenia and leucopenia

5- Criteria for diagnosis

- Splenomegaly > 10 cm from the left costal margin + sustained reduction in spleen size of at least 40% on antimalarial treatment

6- Differentiation from splenic involvement by lymphoma

- Difficult without sophisticated techniques, but the diagnosis of malarial splenomegaly is more likely if the patient is < 40 yrs and has a peripheral blood lymphocyte count of less than 10×10^9/L

7- Treatment

- Lifelong treatment is necessary as recurrence may occur if treatment is stopped
- Proguanil 100 mg/day is the drug of choice as it is safe for continued use over many years
- On this treatment, the hemoglobin increases and the spleen slowly shrinks although it may never become impalpable

Visceral leishmaniasis (Kala-azar)

Pathogenesis

1- Cause → leishmania donovani complex
- L. donovani, L. infantum in old world
- L.chagasi, L. amazonensis in new world

2- Infective stage → flagellated metacyclic promastigote (leptomonas form)

3- Source → man - reservoir host (dogs and rodents)

4- Mode of transmission
- Biological transmission by bite of infected female sand fly (Phlebotomus in old world and Lutzomyia in new world) – amastigotes (leishmania forms) taken during blood meal → promastigote in the midgut
- Transmission via blood transfusion, infected needles or syringes and congenitally may occur

5- After the leptomonas are engulfed by local macrophages → they pass to blood and all viscera including RES [spleen, liver, lymph nodes, bone marrow and small intestine]

6- Incidence and distribution
- Infants → Mediterranean region (leishmania infantum)
- Children → China
- Young adults → India and Africa
- 90% من الحالات فى العالم تحدث فى بنجلاديش, الهند, نبال, السودان والبرازيل

Clinical features

1- Incubation period → usually 2-6 mo (range: 10 days to > 10yrs)

2- Male to female ratio → 3:1

3- **Leishmanioma** [uncommon at presentation]
- Painful papule at the site of bite (rarely noted)
- Cause → leptomonas engulfed by local macrophages and leishmania form start multiplication

4- <u>Acute presentation</u>

- Onset usually insidious
- Low grade fever
- Progressive splenomegaly, hepatomegaly and lymphadenopathy (esp. in Africa)
    - The liver and spleen →usually firm, regular and non-tender
    - Splenomegaly may be massive (dragging discomfort or less commonly, acute pain due to splenic infarcts)
    - No adenitis
- Anemia, epistaxis, cough, anorexia, wasting, hypotension and loss of hair
- Increased pigmentation in persons with dark skin esp. in India (dusky pigmentation- black fever-)

5- Some patients presents acutely with an → abrupt onset of high swinging fever and other **<u>symptoms resembling malaria</u>** as sweating after each paroxysm [irregular, saddle shaped (rise twice in 24 hrs)]

6- <u>Chronic VL</u>

- May have visited traditional healers and have subjected to medicinal cuts that subsequently become infected
- Infection and ulceration of other wounds is common
- Intercurrent infections → such as, pneumonia, TB, bacillary or amoebic dysentery and cancrum oris are important in long standing disease
- Hepatocellular damage, jaundice, malnutrition, bleeding, nephritis and uveitis

7- <u>Post kala-azar dermal leishmaniasis</u> (PKDL) → may occur following treatment ®

8- <u>Viscerotropic leishmaniasis</u>

- Splenomegaly and fever caused by L.tropica was noted in American troops
- Splenomegaly not massive and no other features typical of VL

9- <u>VL and HIV coinfection</u>

- Atypical presentation
- 90% have CD4 counts < $200x10^6$/L
- Dysphagia and cutaneous or mucocutaneous lesions
- Nodular or ulcerative lesions may affect the tongue, esophagus, stomach, rectum, larynx or lungs

10- <u>Case fatality rates of VL</u>

- Treated cases → 0 -50%
- Untreated cases → 85-90%

Differential diagnosis of massive splenomegaly see collections

Differential diagnosis of moderate splenomegaly see collections

Investigations

1- <u>Parasitological evidence</u>

- <u>Identification of amastigotes of L. donovani spp. [The gold standard]</u>
  - Found in splenic aspirates (> 95% positive), bone marrow (> 85%), buffy coat (> 70%) and lymph node (> 65%)
  - Film (Giemsa stain) → leishmania form
  - Culture of aspirate on NNN medium → leptomonas form in +ve cases
  - Contraindications to splenic aspirate
    © Bleeding tendency
    © Portal H TN
    © Splenic hydatid cyst
    © Vascular abnormalities
- <u>PCR</u> → useful in diagnosis and monitoring of relapse in HIV coinfected patients
- <u>Detection of polypeptide fractions of K39 and K26 leishmania antigen in urine</u>
  - Sensitivity and specificity → 96% and 100% respectively

- Has a good prognostic value → antigens not detected in urine 3 weeks after treatment

- Latex agglutination test
  - Detect leishmania antigens in urine and has proved highly sensitive

2- Circumstantial evidence

- CBC → typically shows pancytopenia
- Serum albumin → ↓
- Serum globulins → ↑ esp. IgG
- Alkaline phosphatase → ↑ in about 40%
- ALT, AST, bilirubin → mild elevation in 20%
- Albuminuria is common
- The formol gel test (FGT)
  - Not specific for VL, and when +ve , indicates hyperglobulinaemia, whatever the cause
  - Principle → add one drop of concentrated formalin solution to 1 ml of serum and shake well → if the test is +ve, the serum becomes a firm opaque jelly (like a cooked egg white) after 20 min at room temp.
- Leishmanin skin test (Montenegro) → -ve , but becomes positive within 2 months following treatment in 75% of cases (due to development of antibodies)

3- Serological evidence

- IFAT and ELISA → > 95% sensitivity and specificity
- Direct agglutination test
- K39 test (immunochromatographic strip test that uses recombinant leishmanial antige)
  - Serology may remain +ve for yrs following successful treatment
  - Serology +ve in only 50% of patients with HIV coinfection

Treatment

1- Prior to treatment

- Treatment of inercurrent infections
- Improving the patient's nutritional status
- Blood transfusion as needed

2- Pentavalent antimonials (SbV)

- Considered 1st line treatment
  - Sodium stibogluconate (Pentostam)
  - Meglumine antimonate (Glucantime)
- Dose
  - 20 mg /kg/day for 20 – 40 days, depending on the geographical region
  - Slow I.V (minimum of 5 min) or I.M injection
  - A rest period of 1 week is recommended after the first 10-14 doses
- Side effects
  - Arthralgia
  - Nausea, abdominal pain
  - Pancreatitis
  - Cardiotoxicity → with prolonged high dose regimens (ST inversion, prolonged QTc interval and fatal arrhythmias)

3- Amphotericin B

- Considered the 2nd line treatment
  - Used in regions with high resistance to antimonials (SbV), such as Bihar and India Or if antimonials not appropriate
- Dose
  - 0.1 mg/kg/day and gradually increasing to 1 mg/kg/day until a total dose of 20 mg /kg has been given
  - Slow I.V. infusion in 5% dextrose over 4 – 6 hr
- Side effects
  - Anaphylaxis, fever, chills, bone pain and thrombophlebitis
  - Renal impairment, hypokalemia and anemia

4- Liposomal amphotericin B (AmBisome)

- Advantages
  - Amphotericin toxicity is reduced and efficacy enhanced by lyophilizations
- Dose for immunocompetent patients
  - 3 mg/kg/day on days 1-5, 14 and 21
  - I.V infusion
- Dose for immunocompromised patients with HIV
  - 4 mg/kg/day on days 1-5, 10, 17, 24, 31 and 38
  - I.V infusion
- The relapse rate is high suggesting that maintenance treatment may be required

5- Pentamidine

- Considered the 2nd line treatment
  - Used in regions other than india where there is no significant resistance to antimonials
- Dose
  - 4 mg/kg on alternate days for 5 – 25 weeks
  - Deep I.M injection
- Side effects
  - Toxicity is common (sudden hypotension following injection, acute hypoglycemia, renal impairment and arrhythmias)
  - Irreversible insulin dependent diabetes occurs in > 10%

6- Miltefosine

- Considered the 1st highly effective oral treatment for VL
- Dose
  - 100 mg /day (or 2.5 mg/kg/day in children) for 4 weeks → 95% cure rates
  - Oral
- Side effects
  - GIT upset
  - Abortion, teratogenicity and male infertility

7- **Aminosidine (paromomycin)**

- Dose → 15 -20 mg/kg/day I.M for 21 days
- Can be used synergistically with SbV or pentamidine → allowing shorter duration of treatment

8- **Splenectomy in resistant cases** → hazardous and best avoided. Such patients die from intercurrent infections

Post-Kala-azar dermal leishmaniasis

Incidence

1- **In India** → occurs in 10% of patients 2-10 years after treatment for VL

2- **In Southern Sudan** → occurs in > 50% at a mean of 56 days (range 0-18 days) following treatment

Clinical features

1- Macules and papules → appear around the mouth, then gradually spread over the face and sometimes over the trunk and limbs

2- In time, nodules may develop → resembling lepromatous leprosy

3- Papules and nodules → usually packed with amastigotes and the patient may act as an important reservoir of infection (the condition may persists > 20yrs)

Treatment

1- PKDL in Africa → **resolve spontaneously** without specific treatment

2- Prolonged treatment with SbV or other drugs may be required to eliminate infection

Cutaneous leishmaniasis

Old world cutanaeous leishmaniasis

Pathogenesis

1- Causative organisms

- L.tropica complex (L. tropica, L.major, L.aethiopica)

2- Infective stage → leptomonas form

3- Reservoir host

- L. tropica → dogs
- L.major → rodents

4- Mode of infection → biological transmission by female phlebotomus

L tropica [dry or urban cutaneous leishmaniasis]

1- Distribution

- Middle east, Africa, Asia, miditerranian region in over populated areas as big cities (urban)

2- Clinical features

- Lesion develop in exposed parts of the body (face, limbs)
- Leptomonas → macrophage → leishmania → multiply → destroys the host cells → granulomatous reaction (nodule)
- Localized nodule which is dry and ulcerates only after several months → ulcer with sharp cut edges and raised indurated margin and scanty exudates (oriental sore قرحة مدنية) → heal by scar
- 2ry bacterial infection is common
- The lesion run chronic course in untreated patients
    - Long I.P. → 2-12 months
    - Delayed ulceration, scanty exudates, slow healing (12 months if untreated)
- Resistance to re-infection with the same species (L.tropica or L.major) following a primary infection is strong and long lasting

L major [wet or rural cutaneous leishmaniasis]

1- Distribution

- Middle east, Asia, Africa in lightly inhabited areas as villages at the edge of desert (rural)

2- Clinical features → as L.tropica but

- Acute course
- Short I.P. (2-6 weeks)
- The lesions occur primarily in the lower limbs
- Rapid ulceration
- The lesions are moist with serious exudates
- There may be 2ry bacterial or satellite lesions
- Rapid healing (3-6 months)

L aethiopica [diffuse cutaneous leishmaniasis]

1- Distribution

- East Africa

2- Clinical features

- Begins as a single nodule in exposed areas
- Then spreads to involve large areas of the skin like lepromatous leprosy
- Usually in patients with impaired cell mediated immunity but it is also the characteristics of the parasite itself

New world cutaneous leishmaniasis [American leishmaniasis]

Pathogenesis

1- Causative organisms

- L.braziliensis complex
- L.mexicana complex

2- Infective stage → leptomonas form

3- Reservoir host → dogs, cats and forest rodents

4- Mode of transmission → biological transmission by female Lutzomyia species

5- Distribution → central and south America

L. brazilliensis [mucocutaneous leishmaniasis – espundia]

1- Uta

- Caused by L.peruviana. There may be one or a small number of skin lesions that are self healing similar to L.tropica

2- Primary skin lesion

- Nodule → ulcer with raised indurated margin → heal by scar in months

3- 2ry or metastatic lesion

- Leishmania → blood or lymph from 1ry nodule → mucocutaneous junctions (mucosa of nasal septum, lips, palate, nasopharynx, larynx → edema, extensive destruction and 2ry bacterial infection → great deformity (Espundia) and death from septicemia or bronchopneumonia

L. Mexicana [Chiclero ulcer or Bay sore]

1- Usually **single small nodule** in the face or ear → ulcerate → heal in 6 months

2- Lesion in the ear → destruction of the cartilage seen in chicleros who live in forests and collects gum from chicle trees

3- Rarely, it causes **diffuse cutaneous lesions** with nasopharyngeal mucosal involvement and regional lymphadenopathy

4- L.pifanoi → the initial lesion is single then spreads slowly like lepromatous leprosy and does not ulcerate or heal

Diagnosis of OWCL, NWCL

1- Clinical

2- Detection of the parasite

- Examination of material obtained by aspiration of fluid or biopsy from the indurated **edge of the ulcer** (scrapings taken from the ulcer surface usually –ve as the organisms destroyed by 2ry infection)
    - Film → leishmania form inside the macrophages (amastigote) (numerous in the early than in the late lesions)
    - Culture on N.N.N medium → leptomonas form (promastigote)

3- Montenegro test

- It is an intradermal test using antigen from cultured promastigotes

- It is +ve in > 95% of infections
- It gives a delayed reaction that appears as an indurated area after 3 days

4- Serological tests

Treatment [doses as before]

1- Before treatment, the following should be considered

- The number, size, evolution and persistence of lesions
- The location of lesion(s) e.g. on the face
- Whether the patient is at risk of ML
- Other features e.g. the presence of nodular lymphangitis

2- Cosmetically unimportant lesions

- Caused by non-destructive and non-metastasizing species usually heal spontaneously and therefore may not require active treatment

3- Local, topical and physical treatments

- Heat treatment or cryotherapy
- Topical amphotericin B (L.major)
- Intralesional antimony therapy
- Paromomycin ointment (available in israel) → may result initially in increased ulceration, so it is best avoided for ulcers on the face

4- Oral treatment

- Indications → relatively benign cosmetically unimportant lesions
- Drugs
    - Ketoconazole → modest activity against L.mexicana, L.(V.)panamensis and possibly L.major
    - Itraconazole → less effective against the Viannia subgenus and L.major
    - Fluconazole → variable effectiveness against L.major
    - Miltefosine → currently being investigated for treatment of New World CL (toxic drug)

5- Parenteral treatment

- Pentavalent antimony therapy (sbV) i.v. or i.m. still the best option if optimal effectiveness is important
- Short course pentamidine
    - Effective in Colombia where the disease is predominantly caused by the viannia sub-genus
- Old World DCL
    - Combination of sbV and aminosidine
    - Response may be poor in some parts of Ethiopia and pentamidine is used as alternative [4 mg/kg/day i.m. for 10 days] ; however, about 10% of patients are left with DM following treatment
- New World DCL
    - SbV
- Leishmaniasis recidivans
    - Parenteral or intralesional sbV
    - Or may respond to heat treatment
- Mucosal leishmaniasis
    - Harder to treat than cutaneous lesions and becomes increasingly so as it progresses
    - sbV 20 mg/kg i.v. /i.m. for 28 days → cure rates about 75% for mild disease and 10-63% for more advanced disease
    - Or conventional amphotericin B
    - Concomitant corticosteroids are indicated if respiratory compromise develops

6- Choosing the most appropriate treatment

- The key questions are who needs parenteral treatment and for how long?
- It is useful to classify clinical presentations as simple or complex based on the following criteria

- Complex → > 2-3 lesions, > 40 mm diameter, lymphatic/lymph node spread, cosmetic problems, functional problems, failure to respond to treatment as a simple lesion

- Patients with complex lesions and all patients with viannia sub-genus species or unidentified New World species should be offered parenteral sodium stibogluconate SSG as first line management
- Summary of recommended 1st line treatment for cutaneous leishmaniasis

Species	Simple presentation	Complex presentation
Old world species	Intralesional, topical, physical or appropriate oral treatment	SSG 20 mg/kg i.v. for 10-20 days
L. Mexicana complex	As above	SSG 20 mg/kg i.v. for 20 days (28 days for patients with mucosal leishmaniasis)
L. viannia sub-genus or unidentified new world species	SSG 20 mg/kg i.v. for 20 days	

7- Prevention

- In middle east, it is customary for mothers to expose cosmetically unimportant areas of their infants to sandfly bites or to deliberately inoculate them with infected material to render the child immune to that species
- A vaccine using live attenuated L.major promastigotes has been produced which appears to be effective although its use carries a small risk of precipitating an aggressive lesion or the development of LR

Trypanosomiasis

Sleeping sickness (African trypanosomiasis)

Trypanosoma gambiense (west)

Pathogenesis

1- Infective stage → short stumpy metacyclic trypanosomes

2- Source of infection

- Man
- Reservoir host → domestic animals (cattle, pigs, goats)

3- Mode of transmission → by bite of Glossina palpalis (tsetse fly)

- Mechanical on proboscis in interrupted feeding
- Biological (organism → crithedia form → short stumpy → inoculative infection after bite by 20 days)

Clinical features [chronic disease ch. by the following successive stages (≥ 3 y)]

1- I.P. → 14 days or more

2- Trypanosomal chancre → indurated painful nodule at the site of bite which lasts 1-2 weeks

3- Parasitaemia

- Irregular fever, headache, joint and muscle pains and rash

4- Invasion of L.Ns

- The trypanosomes are present in the blood, LN and bone marrow
- Generalized lymphadenopathy esp. those of the posterior cervical region (Winterbottom sign)
- HSM
- Generalized weakness, irregular erythematous rash, anemia and leucopenia

5- Invasion of CNS

- Mechanism: trypanosomes gradually invade the CNS → perivascular cellular infiltration → ischemia, petechial hemorrgages and atrophy of nerve cells → chronic diffuse meningoencephalitis and meningomyelitis
- Features: mental dullness and apathy عبط, emaciation تسنح, slow speech, tremors, involuntary movements, convulsions, paralysis. Lastly the sleeping stage نوم develops and the patient falls into coma
- Death occurs either from the disease or from intercurrent infections

Diagnosis

1- Clinical

2- Detection of trypanosomes

- Fluid aspirated from chancre, blood, L.N, CSF
    - Microscopic examination of stained and unstained films
    - Culture on Weinman's medium
    - Animal inoculation: usually fails unless the animal is irradiated to decrease its immunity

3- Serum or CSF IgM → always ↑ due to antigenic variation of the surface coat of the organisms

Trypanosome rhodesiense (East)

Pathogenesis

1- Infective stage → short stumpy metacyclic trypanosomes (the nucleus shifted posteriorly in a small percentage of the short stumpy form when inoculated in animals)

2- Reservoir host → wild game animals

3- Mode of transmission → by Glossina morsitans

Clinical features

1- I.P. → short

2- Bouts of fever and rigors are more frequent ans severe

3- More acute and fatal course

- CNS is involved early and untreated patient usually die within 9 months to one year even befor CNS involvement يعنى بيموت قبل ما ينام

4- Untreated cases → severe toximeia → prominent myocarditis and emaciation

5- Higher parasitemia

- Trypanosomes appear in blood early in infection and in considerable numbers

Diagnosis → as gambiense

1- But trypanosomes are more frequently found in blood and are more readily detected on animal inoculation into rats and mice with the appearance of posterior nucleated forms

Treatment → as gambiense

1- But it is more resistant and requires earlier and more intensive treatment

Why East more dangerous than West African trypanosomiasis الشرق اخطر

© Higher parasitemia

© Acute course

© Myocarditis

© Resistant to treatment

Chagas' disease (American trypanosomiasis)

Trypanosome cruzi

Pathogenesis

1- Infective stage → short stumpy metacyclic trypanosomes

2- Source of infection

- Man
- Reservoir host → domestic and wild animals

3- **Mode of transmission**

- Biological transmission by Triatoma (winged bug)
  - Contaminative infection → contamination of the skin abrasions and mm by faeces of winged bugs
- Congenital
- Transfusion of infected blood
- Infected mother's milk

4- Metacyclic trypanosomes multiply as leishmania form in the macrophages at the site of entery → **Chagoma**

5- The parasites enter the **blood** as trypanosomes → invade RES, myocardium, skeletal muscles and CNS (multiply as leishmania destroying these cells)

Clinical features

1- **Acute form usually in children**

- High fever, muscle pain wnd exhaustion
- Epistaxis is common
- Chagoma → erythematous indurated area more frequently on the face
- Romana's sign → sudden unilateral edema of the upper and lower eyelids and cheek usually with conjunctivitis
- HSM and lymphadenopathy
- Rarely skin rash may occur

- In severe infections → Meningoencephalitis or myocarditis and heart failure
- Death may occur or the patient may recover or pass to the chronic stage

2- <u>Chronic form usually in adults</u>

- Heart → ECG changes, myocardial fibrosis and heart failure
- Less commonly invasion of CNS (paralysis) or the thyroid gland
- Megacolon → constipation
- Megaeosophagus → dysphagia
- Immunosuppression due to drugs or AIDS results in exacerbation of infection

Diagnosis

1- Clinical

2- <u>Detection of trypanosomes</u>

- Examination of blood for trypanosomes during febrile periods
  - Direct thick smear
  - Culture on NNN medium
  - Animal inoculation
- Examination of aspirate (biopsy) for leishmania form (amastigotes)
  - LN, liver, spleen and bone marrow

3- <u>Serological tests</u>

- IHA, ELISA, IFA

4- <u>Intradermal alergic test</u> → Cruzin test

5- Xenodiagnosis: feeding laboratory bred winged bug on the suspected patient's blood then examining the gut of the bug for trypanosomes

6- PCR

Treatment of African trypanosomiasis

General measures

1- It is important to treat coexisting **infections and anemia** prior to specific treatment

2- Many advocate routine **antihelminth and antimalarial** therapy

3- Improving general condition

Early stage disease

1- **Suramin** [early = not penetrate CSF]

- Indications
  - Drug of choice for treating early stage T. rhodesiense infection
  - It is also effective in early T. gambiense infection but not the first choice
- Administration and doses
  - Following a test dose of 5 mg/kg → 20 mg/kg (max. 1g) should be given I.V. on days 1, 3, 10, 17 and 24
- Side effects
  - Usually well tolerated, but fever, nausea and proteinuria may occur
  - Infrequent idiosyncratic anaphylactic reactions may occur

2- **Pentamidine** [early = not penetrate CSF]

- Indications
  - Drug of choice for early T. gambiense infection
  - Also effective in early stage T. rhodesiense infection
- Administration and doses
  - 4 mg/kg/day I.M or I.V. for 7-10 days
- Side effects
  - Painful local tissue reaction with i.m. injection
  - Syncope, hypotension and hypoglycemia may occur

Late stage disease

1- Melarsoprol

- Indications
  - Late stage T.gambiense and T. rhodesiense infections
- Effect → active against blood, tissue and CNS trypanosomes
- Administration and doses
  - Treatment preceded by 1-2 doses of suramin to clear blood, lymph and tissue trypanosomes
  - There are many different treatment schedules but it is normally administered as 3 or 4 series of 3 injections (i.v.) separated by 7 days at doses that range from 1.2 to 3.6 mg/kg
  - Recent studies suggest that shorter 10 day courses (2.2 mg/kg daily) may be as effective for T.gambiense infection
- Side effects
  - Serious reactive arsenic encephalopathy → incidence 2-10% and case fatality rate up to 50%. Prophylactic corticosteroids and improving general condition reduce the risk of encephalopathy in T. gambiense infection
  - Peripheral neuropathy

2- Eflornithine

- Indications
  - Effective only against late T.gambiense infections (can be used in early disease)
- Administration and doses
  - 400 mg/kg/day i.v. infusion in 4 divided doses for 14 days [may be followed by 300 mg/kg/day orally in 4 divided doses for 3-4 weeks]
- Side effects
  - It is relatively expensive and difficult to administer but less toxic than melarsoprol

- The common side effects (GI symptoms and anemia) do not usually require treatment to be stopped

3- Nifurtimox

- Used in Chagas' disease but there is emerging evidence of its efficacy for treating T.gambiense in combination with eflornithine or melarsoprol

Monitoring cure

1- Patient symptoms should resolve after treatment

2- Full cure cannot be assumed unless a **2 year follow up** has been completed

3- Despite the severity of the symptoms in advanced late cases, the degree of functional recovery after successful chemotherapy is remarkable

4- Parameters of cure [may take 6 months]

- Fall of CSF cell count below $5/mm^3$
- Normal protein concentration

  Failure of these parameters to reach normal may be the 1st indication that treatment has been unsuccessful

5- Delayed treatment of CNS involvement

- Result in persistant neurological defects
- Most commonly take the form of intellectual impairment

Relapse

1- T.gambiense relapse after suramin or pentamidine

- Often treated with melarsoprol
- Eflornithine can also be used

2- T.rhodesiense

- Usually treated with a 2nd course of melarsoprol

Treatment of American trypanosomiasis

Acute stage

1- Nifurtimox

- Indications → The drug of choice in treatment of acute and early chronic cases
- Dose
  - 15 mg/kg/day in 3 divided doses for 1-3 months
- Effect
  - It inhibits intracellular development of T.cruzi (suppress parasitemia)
  - Shorten the course of the acute illness
  - Prevent acute neurological and myocardial complications
- Elimination of parasites and prevention of chronic disease only occurs in 50-80% of patients

2- Benznidazole → as Nifurtimox

3- Primaquine

- Dose → 15 mg/kg/day for 14 days
- Effect → can destroy trypanosomes in the blood and thus reduce further tissue invasion in the acute stage

Indeterminate and chronic phase

1- Intermediate phase

- Benznidazole may clear parasitemia in some patients and may prevent progression to chronic disease

2- Chronic phase

- Value of parasitological treatment remains uncertain but may prevent progression

3- Cardiac complications

- Symptomatic treatment
- Insertion of pacemakers is often necessary

Amoebiasis

Pathogenesis

1- Infective stage → mature 4 nucleated cysts (resistant to gastric HCL)

2- Source of infection

- Man: asymptomatic carrier and chronic cyst passer (acute cases not infective –trophozoite- can't resist HCL)
- Reservoir host: dog, pigs and monkeys

3- Habitat → large intestine (the wall and lumen of the colon esp. the caecum and sigmoido-rectal region)

4- Mode of infection

- Autoinfection → faeco-oral route
- Heteroinfection through
  - Eating raw vegetables contaminated with human faeces
  - Drinking water contaminated with human excreta
  - Flies and cockroaches carrying cysts to food or drink
  - Food handlers esp. chronic asymptomatic cyst carriers

5- Pathogenesis

- There are 2 groups of E. histolytica trophozoites
  - Pathogenic or tissue form which invade the mucosa and submucosa
  - Non pathogenic or lumen form
- Both types are similar morphologically and they can interchange under certain conditions
- The pathogenic activity of E.histolytica depends upon:
  - Virulence of organisms
  - Resistance of the host
  - Condition of the intestinal tract → physical or chemical injury, carbohydrate diet, stasis and bacterial flora increase the extent of intestinal invasion
- Penetrate laterally by lytic enzymes

- Flask shaped ulcers with deeply undermined edges
- Site → common in caecum, pelvic colon, rectum and flexures. At these sites the flow of intestinal content is slow giving chance for the organisms to invade the wall
- This is followed by
    - Proliferation of connective tissue which ultimately causes fibrous thickening of intestinal wall
    - Intensive ulcerations are invariably accompanied by 2ry bacterial infection
    - Extraintestinal invasion by passage of trophozoites via portal blood may occur

Clinical features

1- I.P. → few days to many years

2- Asymptomatic infections

- It is the most common type where the organisms live in the lumen of the colon as commensals with no tissue invasion
- The person is healthy but the cysts are found in the stool (cyst passer)

3- Intestinal amoebiasis

- Acute amoebic dysentery [acute or more gradual onset of colitis with]
    - Diarrhea with mucus and blood. Bloody diarrhea may occur
    - Tenesmus, flatus and abdominal discomfort and pain
    - Tenderness over the caecum and sigmoid colon
    - Painful spasms of the anal sphincter is a sign of rectal ulcerations
    - The right iliac pain may simulate acute appendicitis
    - The general condition is good but headache, nausea and anorexia may occur
- Chronic intestinal amoebiasis
    - Recurrent short attacks of diarrhea or dysentery alternating with normal bowel habits
    - Abdominal distension with constipation may occur
    - In long standing infections there is loss of weight and cachexia

4- Extraintestinal amoebiasis

- Amoebic hepatits → enlarged tender liver with pain in the right hypochondrium
- Amoebic liver abscess → see hepatology
- Pulmonary amoebiasis
    - Fever, leucocytosis and evidence of consolidation
    - Trophozoites may appear in the sputum in case of amoebic abscess eroding a bronchus
- Less commonly brain, skin and other organs

5- Complications of intestinal amoebiasis

- Perforation and Peritonitis → abrupt/insidious onset; may occur after the patient has commenced treatment
- Haemorrhage → due to erosion of a large blood vessel in the wall of the ulcer resulting in anemia or shock
- Stricture → esp. of the colon and rectum
- Post-dysenteric ulcerative colitis → mimicking classical ulcerative colitis; usually resolves slowly without specific treatment; rarely progresses to massive necrosis and toxic megacolon
- Skin ulceration → usually perianal and anogenital regions, but may occur elsewhere for example in surgical wounds and ileostomy/colostomy sites
- Amoeboma → chronic inflammatory mass of the intestinal wall around the ulcer, single or multiple, most commonly developing in the ileocaecal region presenting as an acute/subacute obstruction or causing an intussusceptions or in the rectosigmoid region
- Appendicitis

Differential diagnosis of amoebic colitis

1- Causes of dysentery or bloody stools

- Shigella
- Typhoid and other salmonella
- E.coli (enteroinvasive and enterohaemorrhagic)

- Schistosomiasis (esp. mansoni and japonicum)
- Balantidium coli
- Trichuris trichiura
- Tuberculosis
- Carcinoma
- Inflammatory bowel disease
- Ischemic colitis
- Diverticulitis
- Arteriovenous malformation

2- Causes of acute or chronic abdominal pain

Differential diagnosis of amoeboma

1- Tuberculosis

2- Carcinoma

3- Actinomycosis

4- Appendix mass

5- Antibioma

Investigations

1- Clinical

- Acute amoebic dysentery should be differentiated from bacillary dysentery which is characterized by its acute onset, high fever, leucocytosis and type of stool

2- Type of stool

- Amoebic stool → bulky, offensive, acidic with scanty leucocytes, blood, epithelial cells, Charcot Leyden crystals and amoebae
- Bacillary dysentery stool → alkaline, scanty faecal matter with massive cellular exudates, pus cells, blood with no Charcot Leyden crystals and no amoebae

3- Stool examination (microscopy)

- Freshly passed loose stools → trophozoites containing ingested RBCs (non pathogenic amoebae do not contain ingested RBCs)
    - The stool sample should be examined within 15 min or should be maintained at body temperature until examined as trophozoites

lose their motility and tend to round up as the specimen cools, thus becoming more difficult to identify

- Formed stools → for cysts (resemble that of E.dispar)

4- Sigmoidoscopy

- Help in patients with suspected intestinal amoebiasis in whom stool microscopy or antigen tests are negative, however it is an invasive method
- Bowel preparations with enemas or cathartics is not advised because this may interfere with the identification of the parasite
- In acute cases → discrete patchy ulceration with a granular friable mucosa
- In more chronic disease → large flask shaped ulcers with loosely adherent yellowish or grey pseudomembranes
- Aspirates, scraping or superficial biopsy from the ulcer edge → may show motile erythrophagocytic trophozoites if examined immediately and should also be positive when tested for antigen
- The parasites are readily identified by their magenta colour in biopsy specimens using a periodic acid Schiff stain
- The endoscopic appearance of amoebic colitis resembles that of IBD and misdiagnosis may occur. Also, E.histolytica may invade areas of the bowel affected by other pathology such as carcinoma leading to diagnostic confusion

5- **Serology** → see hepatology

- Indirect haemagglutination assay is the most sensitive
- 10-35% of people living in developing countries have +ve serology

6- **Imaging** → see hepatology

- Barium enema → may demonstrate areas of ulceration, stricture or a filling defect from an amoeboma; however, non of these appearances are specific for amoebiasis and there is a risk of perforation in patients with severe disease

7- **Aspiration** from lung or liver abscess → see hepatology

8- Detection of E.histolytica antigens:

- In stools using monoclonal antibody and immunoassay is more sensitive and specific and can differentiate between E.histolytica and E. dispar
- In pus from ALA

Treatment

1- <u>Invasive amoebiasis</u> [one of the following tissue amoebicides usually effective]

- <u>Metronidazole</u>
  - Adults → 800 mg 3 times daily orally for 5-10 days
  - Children → 35-50 mg/kg/day in 3 divided doses for 5-10 days
- <u>Tinidazole</u>
  - Adults → single oral dose of 2 g is better tolerated and should be continued for 3-6 days in case of more severe infections
  - Children → 50-60 mg/kg/day for 3-5 days
- <u>Oral chloroquine</u>
  - Adults → 600 mg base daily for 2 days followed by 300 mg base daily for 2-3 weeks is also effective in the treatment of amoebic liver abscess
  - Children → 10 mg/kg/day (max. 300 mg/day base) in 2-4 divided doses for 2-3 weeks

2- <u>Eradication of cysts</u> [one of the following luminal amoebicides]

- <u>Diloxanide furoate</u>
  - Adults → 500 mg orally 3 times daily for 10 days
  - Children → 20 mg/kg/day in 3 divided doses for 10 days
- <u>Paromomycin</u>
  - Adults and children → 25-35 mg/kg/day in 3 divided doses for 7 days
- <u>Iodoquinol</u>
  - Adults → 650 mg 3 times daily for 20 days
  - Children → 30-40 mg/kg/day (max. 2 g) in 3 divided doses for 20 days

- Quinfamide
    - Adults and children → 3 doses of 100 mg each in a single day (full prescribing information is not yet available)
- Tetracycline : may also be used

3- Principle of treatment and follow up

- A 5 day course of metronidazole is usually sufficient for the treatment of amoebic dysentery and most other forms of invasive amoebiasis
- It is usuall to follow on with a course of a luminal amobecide, but if unavailable, patients with severe infections should be given a 10 day course of metronidazole
- Patients treated with tinidazole or chloroquine should also receive a luminal amoebicide
- Stools are re-examined 4 weeks later

4- Nitazoxanide

- Thiazolide compound which has been shown to be well tolerated and effective in treatment of wide range of GI infections in both adults and children
- Dose : 3 day oral course
    - Adults and children > 12 y → 500 mg b.d.
    - Children 4-11 y → 200 mg b.d.
    - Children 1-3 y → 100 mg b.d.
- Indications
    - E.histolytica (tissue and luminal)
    - G.lamblia
    - Blastocystis hominis
    - Isospora belli
    - Cyclospora cayetanensis
    - Dicrocoelium dendriticum
    - Cryptosporidium parvum
    - Trichomonas vaginalis
    - Balantidium coli
    - Ascaris lumbricoides
    - Strongyloides

- T. trichiura
- Enterobius vermicularis
- T.saginata
- H.nana
- Fasciola hepatica
- Clostridium difficile
- Helicobacter pylori
- Rotavirus
- Norovirus

5- Asymptomatic cyst passer

- Ideally, one should differentiate between E. histolytica and E. dispar (commensal) using stool antigen test (not available in resource poor setting)
- In endemic areas → the value of treatment is questionable because of reinfection
- It is important to eliminate E.histolytica prior to immunosuppressive treatment as this may exacerbate amoebic colitis and lead to extension into the perineum or into the abdominal wall → either 5 day course of metronidazole (or single dose of tinidazole) followed by a luminal amoebicide or a 10 day course of metronidazole

6- Severely ill patients

- Parenteral metronidazole + gentamicin + 3rd generation cephalosporins or ampicillin to cover 2ry sepsis from bowel pathogens
- Management of fluid and electrolyte disturbances, anemia, ileus and other complications

7- Treatment of complications

- Amoebic liver abscess → see hepatology
- Amoebomas
    - Usually respond rapidly to medical treatment and failure should raise suspicion of coincidental pathology such as a carcinoma
    - Surgery may be indicated in cases of obstruction or intussuception
- Acute colonic perforation

    - Surgery recommended if no diffuse colitis (because the bowel is very friable and difficult to repair or anastomose)
    - However, toxic megacolon or abdominal abscess should be managed surgically
- Ruptured amoebic appendicitis → surgery

Giardiasis

Pathogenesis

1- Cause → Giardia lamblia

2- Definitive host → man , occasionally beavers

3- Infective stage → cyst [resistant to chlorination]

4- Habitat → duodenum and upper jejunum, occasionally biliary tract and the stomach in patients with achlorhydria (usually in association with H. pylori)

5- Mode of infection

- Ingestion of cysts in contaminated food, water or hands
- Autoinfection

6- Trophozoites does not invade intestinal mucosa, but attached to it → disrupts the intestinal brush border and interfere with enzyme activity. Also, stimulates an inflammatory cytokine response resulting in secretion of fluid and electrolytes and damage to enterocytes

Clinical features

1- Incubation period → 7 – 10 days [range: 3 days: several months]

2- Asymptomatic in most cases

3- **Clinical symptoms**

- Abrupt onset of diarrhea, abdominal cramps, bloating and flatulence
- Stool → foul smelling, float, soft, watery to greasy with mucus and does not contain blood
- Often associated with malaise, anorexia, nausea and belching accompanied by a taste of rotten eggs
- Symptoms more severe in initial infections and more difficult to treat in patients with impaired immunity

4- **Some** may have significant weight loss (delayed medical advice)

5- **Rarely**, cholangitis and cholecystitis

6- **Clinical course**

- Many, often after periods of fluctuating symptoms, eventually become asymptomatic
- Others, continue to have persistent diarrhea, associated with malabsorption (steatorrhea), malnutrition and failure to thrive [esp. in immunocompromised patients]
- In some patients, chronic diarrhea may be partly related to lactose intolerance → which may persist despite eradication of the Giardia

Differential diagnosis Causes of acute and chronic non-bloody diarrhea and other causes of malabsorption

1- Parasitic

- Fasciolopsiasis, capillariasis, strongyloidiasis
- Isosporiasis and cryptosporidiosis

2- Tropical sprue

3- Hypolactasia

4- Chronic calcific pancreatitis

5- Malnutrition

6- Intestinal TB

7- Alpha-chain disease

8- Celiac disease

9- Small bowel lymphoma

Investigations

1- **Stool examination**

- Detect characteristic cysts [formed stools]
- Motile trophozoites, sometimes seen in saline preparations [loose stools]
- Repeated examination is required, as passage of cysts can be intermittent

2- **Duodenal fluid aspiration and microscopy** [String test] → for trophozoites

3- **Serology**

- ELISA and direct fluorescence antibody techniques
- For rapid detection of Giardia antigen in stool samples

4- **A panel EIA test**

- Detect Giardia, E.histolytica and Cryptosporidium parvum with sensitivity and specificity > 95%
- However, antigen testing should not replace stool microscopy because other pathogens may be present and may be responsible for the patient's symptoms

5- **Small bowel biopsy**

- Useful in patients in whom an alternative or concurrent diagnosis is possible
  - Suspected tropical sprue
  - HIV
  - Common variable immunodeficiency
- Typical findings of giardiasis
  - Villous flattening
  - Deepening of crypts
  - ↑ inflammatory infiltrate in the lamina propria
  - Giardia trophozoites, may be seen in the intervillous spaces

Treatment

1- **Oral metronidazole**

- Adult dose → 400 mg three times daily for 5 days **or** 2 g / day for 3 days
- Pediatric dose → 15 mg/kg/day in three divided doses **or** 40 mg/kg/day for 3 days
- Contraindicated in 1st trimester of pregnancy [paromomycin is safe but less effective]

2- **Tinidazole**

- Adults → single oral dose of 2 g
- Pediatrics → 50 mg/kg (max. 2 g) as single oral dose

3- **Albendazole**

- 400 mg/day for 5 days

4- Nitazoxanide

- Effective and have proved useful in treating patients who are HIV positive, who fail to respond to standard treatment

5- **Other drugs** → quinacrine, furazolidone and paromomycin

6- Causes of failure to eradicate the organism

- Poor compliance, reinfection
- Antimicrobial resistance or underlying immunodeficiency

7- Causes of persistent symptoms despite eradication

- Continuing lactose intolerance
- Another etiology and the Giardia was a coincidental finding

Toxoplasmosis

Pathogenesis

1- **Causative agent**

- Protozoal disease caused by toxoplasma gondii
- The organism has a sexual cycle in intestinal epithelium of definitive host (cat family) and asexual cycle in secondary hosts (birds, rodents and humans)

2- **Infective stage** → sporocyst

3- **Mode of transmission**

- Ingestion of tissue cysts in raw or poorly cooked meat
- Ingestion of sporocysts derived from cat faeces contaminating soil or inadequately washed vegetables
- Via organ transplantation
- Transplacental
- Rarely, through blood transfusion because duration of parasitaemia following acute infection is limited

4- **Pathology**

- The effect on organs is due to direct cell invasion by the parasite
- Focal necrosis due to replicating tachyzoites → induce mononuclear inflammation and multiple infarcts in immunosuppressed

Clinical features

1- Incubation period → 1 – 3 weeks

2- **Immunocompetent patient**

- Acute infection may be unnoticed
- Painless cervical lymphadenopathy
    - Single or multiple
    - Discrete
    - Not tender
    - Vary in firmness
- ± fever, malaise and myalgia

3- <u>Congenital infection</u> [transplacental]

- The possibility of transplacental infection ↑ as the interval between infection and contraception ↓ [esp. within 6 months before pregnancy]
- There is no risk if the mother is infected ≥ 6 months before contraception
- If the mother infected during the 1st trimester → the risk of fetal infection is 25% but the disease in neonates is more severe
- 65% of infection is acquired in the 3rd trimester but the infant is usually asymptomatic at birth but may have learning disabilities and chronic neurological sequelae
- If the baby is born with toxoplasmosis infection, he will present with
    - Hydrocephalus
    - Microcephaly
    - Mental retardation
    - Cerebral calcification
    - Retinochoroiditis

4- <u>Ocular toxoplasmosis</u>

- Retinal damage → necrotizing retinitis → appear as white yellow cotton patches in the fundus

5- <u>Toxoplasmosis and HIV</u>

- <u>Cause</u> → reactivation of dormant focus
- <u>Clinically</u>
    - Fever, headache
    - Diminution of mental status
    - Focal neurological signs
    - Encephalitis
    - Retinochorioditis
    - Pulmonary disease (cough, dyspnea, pneumonitis and resp. failure)
- <u>DD</u> → lymphoma, fungus and bacterial infections

6- **Toxoplasmosis and organ transplantation**

- Fever , deterioration of consciousness and respiratory failure occur 3 – 6 weeks after operation

Diagnosis

1- **Blood picture** → lymphocytosis

2- **Liver enzymes** → ↑↑

3- **Parasite detection**

- Isolation of T. from blood or body fluid
  - After subinoculation of the body fluid in peritoneal cavity of mice → acute infection after 3-6 weeks of inoculation
- Isolation of T. from biopsied tissue
  - Is an indication of the presence of the tissue cyst and not considered as acute infection
- Presence of tachyzoites in L.N. → acute infection مهم

4- **Serology**

- Simultaneous presence of IgG, IgM مهم → acute infection (also, IgA)
- Sabin-feldman dye test, indirect fluorescent antibody and ELISA → measure circulating IgG
- In border line ↑ in either IgG or IgM → the titre is assessed every 3-4 weeks
- Immunofluorescent antibody IgM titre 1/600 or rising titre → acute infection مهم

5- **CT scan and MRI** → multifocal and focal abnormalities

Treatment

1- **In immunocompetent with L.N. in adults**

- No treatment unless having severe symptoms
- Therapy for 4 weeks
  - Sulfadiazine 2 g/day +
  - Pyrimethamine (Daraprim) 25 mg/day +
  - Folic acid 15 mg twice/week (as pyrimethamine is a folic acid antagonist and leads to bone marrow depression)

2- Ocular treatment

- Therapy for 4 weeks [for 10 days after improvement of inflammation]
  - Sulfadiazine 2 g /day or clindamycin 1.2 g/day +
  - Pyrimethamine 25 mg/day +
  - Vitamins
- Followed by
  - Systemic steroids
  - Laser or cryotherapy [limit the spread]

3- Congenital (neonates)

- Therapy
  - Pyrimethamine 0.5-1 mg/kg +
  - Sulfadiazine 100 mg/kg for 3 weeks
- Followed by
  - Spiramycin 100 mg/kg/day for 3 weeks
- This rotating treatment till the age of 1 year

4- Pregnant females

- Therapy
  - Spiramycin 3 g /day for 3 weeks followed by
  - Sulfadiazine 50-100 mg/kg/day + pyrimethamine 0.5-1 mg/kg + vitamins
- This rotating treatment till delivery
- Spiramycin reduces transplacental transmission
- Treatment during pregnancy reduces risk of fetal complications

5- With AIDS

- Sulfadiazine 4-6 g/day + pyrimethamine 50-75 g/day + vitamins for 6 weeks
- Dapsone 200 mg/day to prevent relapse or reduce the dose therapy
- Fansidar [pyrimethamine 25 mg + sulfadoxin 500 mg] 2 tab. Twice daily for 2 days then 2 tab. /day for 19 days

6- Organ transplantation

- Pyrimethamine 25 mg as prophylaxis for 6 weeks for seronegative recipients after operation

HELMINTHIC DISEASES

<table>
<tr><th>Hepatic flukes</th><th>Blood flukes</th><th>Lung flukes</th><th>Intestinal flukes</th></tr>
<tr><td>-Fasciola gigantica
-Fasciola hepatica</td><td>- S. hematobium
- S. mansoni
- S. japonicum</td><td>-Paragonimus westermani</td><td>- H. heterophyes</td></tr>
<tr><th colspan="2">Intestinal cestoda –Adult-</th><th colspan="2">Extraintestinal cestoda –Larva-</th></tr>
<tr><td colspan="2">- Diphyllobothrium latum
- Dipylidium caninum
- Taenia saginata
- Taenia solium
- Hymenolepis nana
- Hymenolepis diminuta</td><td colspan="2">- Sparganosis (D. mansoni& proliferum)
- Cysticercosis (T. solium)
- Hydatid cyst (E. granulosus& multilocularis)
- Coenurus cyst (M. multiceps)
- Cysticercoid larva of H.nana</td></tr>
<tr><th colspan="2">Intestinal nematode</th><th colspan="2">Tissue nematoda</th></tr>
<tr><th>Small intestine</th><th>Large intestine</th><th>Adult</th><th>Larva</th></tr>
<tr><td>- Ascaris
- Ancylostoma
- N. Americans
- Strongyloides
- Capillaria
- Trichinella
- Trichostrongylus</td><td>- Enterobius
- Trichuris</td><td>-Dracunculus medinensis
- Filaria
* Wuchereria bancrofti
* Brugia malayi
* Loa loa
* Onchocerca volvulus</td><td>- Trichinella spiralis
- VLM
- CLM</td></tr>
</table>

Soil transmitted helminthes

Definition

The term "soil-transmitted helminthes" applies to a group of parasites whose life cycle usually depends on a period of **development outside the human host**, typically in moist warm soil

Causes

1- **Ascaris** lumbricoides

2- **Ancylostoma** duodenale and nectar americanus

3- **Trichuris** trichiura

4- **Toxocara** canis and toxocara cati

Ascariasis

Pathogenesis

1- Infective stage

- Mature egg with the 2nd stage rhabditiform larva

2- Definitive host → man

3- Habitat → small intestine

4- Intermediate host → no I.H (soil with suitable conditions)

5- Mode of infection

- Ingestion of mature eggs containing the 2nd stage larva with contaminated food (green raw vegetables), water or hands

6- Peak age → 3 -8 yrs

Clinical features

1- Migrating larvae

- **Ascaris pneumonitis**
  - Fever, cough with sputum, dyspnea, wheeze and urticaria
  - In severe cases → chest pain, cyanosis and hemoptysis
  - Associated with eosinophilia in 20% (Loffler's syndrome)

- Symptoms usually resolve spontaneously within 10 days

- **Ectopic sites** via circulation
  - Abnormal clinical manifestations

2- Adult worms

- Abdominal colic, distension, dyspepsia, diarrhea or constipation
- Anorexia or polyphagia
- **Lactose intolerance and malabsorption** of vitamin A and other micronutrients may occure → malnutrion
- **By-products of living or dead worms:**
  - Fever, urticaria, ashma, insomnia or even epileptiform attacks may occur esp. in children
- **Intestinal obstruction or volvulus**
  - By a mass of worms in heavy infections may occur esp. in children
- **Wandering adult worms** may be extensive and possibly pass to:
  - Back to the stomach and are vomited or even withdrawn by the patient from the pharynx
  - Large intestine and expelled from the anus
  - Esophagus, larynx, trachea causing asphyxia
  - Common bile duct causing obstructive jaundice, cholangitis or liver abscess (more common in adults)
  - Common pancreatic duct causing acute pancreatitis
  - Appendix causing appendicitis
  - Rarely, perforation of the intestine causing peritonitis or continue to lay eggs causing granulomatous peritonitis
  - Can make an unwelcome appearance in endotracheal tube or obstruct NGT and even enter the paranasal sinuses

Investigations

1- **Stool examination**
   - May show the ova or even the adult worms
   - May be negative; if all worms are male

2- **Sputum analysis** → show larvae and/or eosinophils

3- **CBC** → eosinophilia (Loffler's syndrome)

4- **Chest X-ray**:
   - Discrete densities to diffuse interstitial infiltrates (ascaris pneumonitis)

5- **Worms may be found by means of**:
   - Barium studies (vermiform translucencies)
   - U/S, upper endoscopy (in the 2nd part of duodenum)
   - ERCP (in the common bile duct)
   - Plain X-ray (may show worms in the gas filled loops of obstructed bowel)

Treatment

1- **Albendazole**
   - **Dose** → 400 mg as single oral dose (clears most infections)
   - **Dose in children** 1-2 yrs → 200 mg
   - Heavey infections may need **repeate**d doses for 2 or 3 days

2- **Mebendazole**
   - **Dose** → 100 mg orally twice daily for 3 days
   - Not recommended < 2 yrs
   - A single dose of 500mg may be effective
   - **Ectopic migration** of ascaris has been reported following the use of mebendazole

3- **Levamisole**
   - **Dose** → 2.5 mg /kg as a single dose may be effective

4- **Pyrantel pamoate**
   - **Dose** → 11 mg/kg (up to a max. of 1 g) as a single dose

5- **Piperazine**

- **Dose** → 75 mg/kg (to a max. of 3.5 g for adults and 2.5 g for children aged 2-12 yr)
- Used only if safer alternatives are unavailable (**serious side effects**)
- Pyrantel and piperazine have antagonistic effects and should never be prescribed concurrently

6- **Nitazoxanide** is also effective

7- **Treatment of ascaris pneumonitis**

- Bronchodilators , steroids and antihistaminic
- Symptoms may be exacerbated by larval death (antihelmintics??)

8- **Treatment of intestinal obstruction**

- **Conservatively** with NGT aspiration, I.V. fluids and antispasmodics
- **Followed by antihelmintic** when the obstruction subsides
- **Laparotomy** may be indicated if this fails
- **Surgical or endoscopic removal** of single worms blocking bile or pancreatic ducts may be necessary for patients who fail to respond to antihelmintic and those with persistent pain or raised amylase

Ancylostomiasis

Pathogenesis

1- Infective stage → ensheated filariform larva

2- Definitive host → man

3- Habitat → small intestine

4- I.H → no (soil)

5- Mode of infection

- The filariform larva penetrates the skin or mm of the mouth due to contact with soil contaminated with human excreta (usually big toes, dorsal surface of the foot and interdigital spaces of the hands)

6- Ancylostoma infection → if poorly nourished patient have large number of worms causing clinical manifestation

7- Ancylostoma infestation → if fairly nourished have small number of worms (asymptomatic)

Clinical features

1- Most infection are **asymptomatic**

2- **Hypochromic microcytic anemia**

- Evident in pregnant women, women with menorrhagia and children
- The cause is chronic blood loss through the intestine (due to sucking of blood and bleeding at the site of attachment)
- Pallor, tachycardia, spooning of nails or even heart failure
- May associated with hypoalbuminemia and edema

3- **Retardation** of physical and mental development

4- **Skin lesions**

- Ground itch (local dermatitis) → may occur at the site of larval penetration and, if severe, may be associated with vesicles or pustules
- Serpiginous rash of cutaneous larva migrans may be seen, although less common

5- **Larval pneumonitis** with eosinophilia (Loffler's syndrome) → during migration of the larva through the lungs

6- **Abdominal** discomfort, flatulence, anorexia, nausea, vomiting and diarrhea, sometimes containing blood and mucus may occur few weeks of heavy infection

7- GIT hemorrhage → reported as a rare complication in young children

8- **Wakana syndrome**

- May follow oral ingestion of A.duodenale larvae
- Nausea, vomiting, pharyngeal irritation, cough, dyspnea and hoarseness

Investigations

1- **Stool examination**

- Detection of eggs by simple smear
    - Mistaken with Ternidens diminutus eggs (causing cystic nodule in the colon and anemia) which are larger than Anc. Eggs

- Mistaken with Trichostrongylus spp. Eggs which have more pointed ends than the eggs of Anc.

- Concentration methods for light infection
- Culture for larvae (mistaken with S. stercoralis larva)

2- CBC

- Microcytic hypochromic anemia
- Eosinophilia is common (during migration of larva)

Treatment

1- Treatment of iron deficiency anemia ® see hematology

- Oral iron (ferrous sulphate or gluconate)
- In severe cases → packed RBCs transfusion may be required

2- Good nutrition with high protein diet and vitamin supplements

3- Albendazole → 400 mg as a single dose is usually effective

4- Mebendazole → 100 mg twice daily for 3 days

5- Levamisole → 2.5 mg/kg as a single dose repeated after 7 days

6- Pyrantel pamoate → 11 mg/kg (max. 1g) for 3 days is also effective

Trichuriasis

Pathogenesis

1- Infective stage → mature eggs with rhabditiform larva

2- Definitive host → man

3- Habitat → caecum, appendix , may extend into ' colon, even rectum

4- I.H → no (soil)

5- Mode of infection → ingestion of mature eggs containing the rhabditiform larva with contaminated food (green raw vegetables, water) or hands

Clinical features

1- Severe GI symptoms resembling inflammatory bowel disease (ulcers, hge and submucosal abscesses at point of attachment)

- Abdominal pain most commonly in lower right quadrant

- Nausea, vomiting, diarrhea with streaks of blood

2- Appendicitis, intestinal perforation and peritonitis

3- **Iron deficiency anemia :**
   - In children on poor diets
   - Due to bleeding from the friable mucosa

4- Growth retardation with chronic infection

5- **Severe trichuris dysentery** syndrome → leads to rectal prolapse

Investigations

1- **Adult worms** can be seen attached to the mucosa of rectal prolapsed

2- **Stool examination:**
   - Detection of eggs by simple smear
   - Conc. Methods for light infection

3- **CBC**
   - Microcytic hypochromic anemia
   - Significant eosinophilia

Treatment

1- **Albendazole** → 400 mg daily for 3 days

2- **Mebendazole** → 100 mg twice daily for 3 days

3- **Single oral dose** of mebendazole 500 mg is more effective than albendazole 400 mg

4- **Single dose combination** treatment using albendazole 400 mg + ivermectin 200 µg/kg is also highly effective

5- **Nitazoxanide** also is effective

Larva migrans

Definition

1- **Migration of larvae** of nematodes in unsuitable hosts, thus, they cannot complete their normal development into adults

2- **Larvae mainly non human larvae**, but sometimes human larvae getting lost in ectopic sites

Types

1- Visceral larva migrans → toxocariasis

2- Ocular larva migrans → [considered visceral] toxocariasis

3- Cutaneous larva migrans

Visceral larva migrans

Definition

1- **Invasion of human viscera** by larvae of dog and cat ascarids e.g. Toxocara canis and Toxocara cati

2- **Some larvae of** Ascaris lumbricoides, Ancylostoma duodenale and Strongyloides stercoralis invade different organs in cases of heavy infection

Mode of infection

1- **Ingestion of mature eggs** in sand or soil contaminated by dog or cat faeces along contaminated foods, water and hands

2- The 2nd stage rhabditiform larva from ingested egg is released in the intestine, which then goes on a prolonged safari **through the tissues**, lasting 1-2 years, and causing eosinophilic granulomatous lesions

Clinical features

1- **Asymptomatic** → with persistent eosinophilia

2- **Symptomatic**

- **Age**

- Mainly children 1- 4 yrs (more likely to come in contact with contaminated soil)

- **General**
  - Fever
  - Abdominal pain and myalgias
  - Lymphadenopathy
  - Eosinophilia
  - Hypergammaglobulinaemia (IgG, IgM)
- **Local**
  - Liver → enlarged tender liver
  - Spleen → splenomegaly
  - Lung → patchy pneumonitis, bronchospasm
  - Brain → sleep and behavioural disturbances, epilepsy or encephalitis
  - Eye → see OLM

Diagnosis

1- **Clinical** → triad of hepatomegally + eosinophilia + hypergammaglobulinemia in a child 1-4 yrs is suggestive

2- **Laboratory**

- Eosinophilia → 20 -80%
- Hypergammaglobulinemia → ↑ IgG, IgM, IgE levels
- ↑↑ anti-A & anti-B isohaemoagglutinins titre (due to cross reactivity with larval antigen)
- Needle liver biopsy(definitive diagnosis) → may show eosinophilic granuloma with demonstration of larva inside it
- Serological diagnosis using ELISA
- Intradermal allergic test
- CBC → anemia

Treatment

1- **The treatment of choice** → albendazole 10 mg/kg/day for 5 days

2- **Alternatives:**

- Thiabendazole → 50 mg/kg/day in 3 divided doses for at least 5 days
- Diethylcarbamazine (Hetrazan) → 3 mg/kg 3 times daily for 21 days

3- **Symptomatic treatment**

- Bronchodilators, steroids or antihistaminic drugs

Ocular larva migrans

Pathogenesis

1- OLM may occur in light infection of **toxocariasis**

2- The larva invades the eye producing a granulomatous reaction, usually in the **retina**

3- The damage usually **permanent** but slight improvement may occur

Clinical features

1- Visual disturbances or sudden blindness in the affected eye

2- May present as strabismus (squint)

3- May go unnoticed and diagnosed on routine ophthalmoscopy

Investigations

1- **Ophthalmoscopy**

- Usually unilateral choroidoretinitis with a mass lesion in the retina, which may be mistaken for a retinoblastoma
- May be slightly raised pale spots

2- Serology usually +ve

3- **Antibody detection in vitreous fluid** is more sensitive and specific

4- Rarely, eosinophilia or evidence of generalized VLM

Treatment

1- Topical or systemic steroids

2- Laser photocoagulation → to destruct the larvae

3- Surgery → for adhesions

4- Antihelmintics → has no additional benefit

Cutaneous larva migrans [creeping eruption]

Definition

1- **Invasion of human skin** by filariform larvae of animal hookworms (dogs and cat) 1.e. Ancylostoma brazilliense and Ancylostoma caninum

2- **Other causes:**

- Filariform larva of non human strain of Strongyloides stercoralis
- Cutaneous myiasis e.g. larva of Gastrophilus fly

Mode of infection

1- The filariform larva **penetrates the skin** due to contact with soil or sand contaminated with dog and cat excreta (eggs)

2- The larvae cannot go beyond the germinal layer but keep migrating in the **epidermis** without further development till they die

Clinical features

1- The lesion started as **red itchy papule** at the site of entry

2- Followed by **typical rash**:

- Slightly elevated very itchy erythematous serpiginous tunnel (track)
- The track don't bifurcate
- The size is 1-2 mm in diameter, with irritation, excoriation and 2ry infection
- Common sites: foot, ankle or hands & may be single or multiple
- Uncommon sites: buttocks → Hookworm folliculitis (pustules)
- The larva advances by only a few mm per day (slowly moving), so the rash is relatively static

3- In contrast, **larva currens** caused by Strongyloides characterized by very rapidly moving linear rash

4- **Rarely the larvae reach the lung** → causing pulmonary symptoms and eosinophilia, but does not mature in the intestine

Treatment

1- **No constitutional disturbance** and the rash will heal spontaneously within a few weeks [the larvae will die even without treatment]

2- However**, treatment indicated due to**

- Severe itching and unpleasant figure
- Some larvae can survive for several months

3- **Older treatment** : [not highly effective]

- Local freezing of the head of the larval track (skin at the advancing end) with ethyl CL spray or carbon dioxide snow → skin bleb and the larvae are lost with epidermal sloughs
- Occlusive application of 10 or 15% thiabendazole in emulsifying ointment

4- **Current options :** [oral treatment are better]

- The drug of choice → albendazole : single oral dose of 400 mg
- Ivermectin → single dose (12 mg for adults)
- Thiabendazole → less effective than albendazole and ivermectin with more side effects (dizziness, nausea and vomiting) ; dose: 25 mg/kg twice daily for 3 days

5- **Antihistamincs** → for itching

6- **Antibiotics** → for 2ry infection

Onchocerciasis [River blindness]

Pathogenesis

1- Cause → onchocerca volvulus (convoluted filaria)

2- Infective stage → microfilaria

3- Definitive host → man

4- Habitat → SC tissue within fibrous nodules, skin and rare in blood

5- I.H → female simulium black flies (day-biting insect)

- Simulium damnosum → in Africa
- S.ochraceum and S. metallicum → in Americas

6- Mode of infection → bite of infected simulium fly

7- Simulium breeds in rapidly-flowing fresh water so Onchocerciasis commonly affects people working at or near fast-flowing rivers

8- Distribution → major cause of blindness in tropical Africa & of skin disease in Africa, Yemen and Central and South America

9- Pathology

- Almost entirely caused by immunological reactions to dying and dead microfilariae and their endosymbiotic Wolbachia which release bacterial mediators that trigger the innate immune system resulting in clinical pathology
- Activated eosinophils release cellular proteins that cause connective tissue damage

10- HIV and oncocerciasis

- Onchocerciasis may ↑ the risk of seroconversion in HIV-1 infection
- Onchodermatitis more severe in HIV- positive patients
- Treatment of onchocerciasis associated with reduced HIV-1 viral replication

Clinical features

1- **Incubation period** → 15-18 mo

2- **Asymptomatic carriers** → for long periods in some people who don't react to microfilaria

3- **Skin manifestations**

- It is common to find several different skin manifestations **simultaneously**
- **Intense itching** → is the principal symptom and leads to excoriation and 2ry bacterial infection
- Asymmetrical maculopapular **rashes** → may be evident
- **Healing** → associated with progressive depigmentation or blackening and thickening of the skin
- **Presbydermia** → gradual development of degenerative skin changes (atrophy) and loss of elasticity giving the skin a wrinkled, prematurely aged appearance
- **Hanging groin appearance** → sometimes, esp. in the presence of inguinal or femoral lymphadenopathy (oncho adenitis)
- **Xeroderma** → dry skin like that of lizard may occur in America
- **Elephantiasis** of external genitalia → may occur due to inflammation and fibrosis of lymph spaces of tissues
- **Leopard skin** → patchy depigmentation, esp. of the lower limbs
- **Sowda** → localized chronic popular dermatitis (hyperpigmentation) due to hyperimmune response (in Yemen, Northen Sudan and West Africa)
- **Subcutaneous nodules**
  * Site: over bony prominences
  * Cause: arrest of migrating SC adult onchocercal worms over bony prominences which are enclosed in fibrous tissue
  * Size and content: 0.5-2.5 cm in diameter and containing a number of live or dead coiled female worms
  * Characters: painless, bean shaped, firm nodules. At first lie free but may later become deeply attached

* Impalpable nodules: may be found in highly endemic regions and need U/S to demonstrate them

* In America: nodules more often found over the head

* In Africa: nodules more often over the pelvic brim, the sacrum, femoral greater trochanters and the medial aspects of the knees

- Skin onchocerciasis is frequently misdiagnosed as **scabies** – the popular eruptions of HIV should be considered

4- Eye manifestations

- **Age :**

* Most patients are blinded in middle life (slowly progressive disese)

* In heavy infections or more virulent strains, blindness can occur in patients in their twenties

- **Risk factors**→ eye lesions is higher with nodules on the head and upper body → leads to invasion of the eye with microfilaria
- **Early disease** → itching, redness, photophobia and excessive lacrimation
- **Late disease** → varying degrees of loss of vision and eventually blindness
- **Anterior eye disease**

* Punctate keratitis → appear as a reversible snow flake opacity (caused by reactions to the death of microfilaria in the cornea)

* Pannus: Forms as blood vessels invade the cornea from the sides and below. The pannus may cover the pupil-sclerosing keratitis- and cause blindness. Particularly among heavily infected individuals in the african savannah

* Iritis → leads to a loss of the pigment frill and to synechiae that cause a deformed, often pear- shaped pupil. 2ry cataract can result

- **Posterior eye disease**

* Chorioretinitis with pigmentary changes

* Often accompanied by optic atrophy (may be the only findings) or neuritis

* Various forms of visual loss may result but a common presentation is with disabling "tunnel vision"

5- **General health**

- Impaired growth → in very heavy infection in adults
- Chronic sleep disturbance, depression and precipitate suicide (due to the unrelenting itch)
- Abandonment of fertile riverside ground in some areas
- Association with convulsions in East Africa??

Diagnosis

1- **Demonstration of microfilaria in aspirate of nodules or skin snips**

- 6 snips needed to be sure of detection
- Skin snips should be taken without blood contamination
- Sites of skin snips
  - Sc nodules
  - In Africa → from the lateral aspects of the calves, thighs, the hip region or the iliac crests
  - In the Americas → from the shoulder tip or outer canthus of the eye because microfilaria tend to concentrate on the upper part of the body

2- Demonstration of adult worms in **excised nodule**

3- Demonstration of microfilaria by Walser **corneo-scleral punch biopsy** (better avoided as it is difficult to keep sharp and sterile)

4- **Slit lamp** → to look for active microfilaria in the anterior chamber of the eye or the cornea after the patient has spent 5 min in a "face down" position to bring the microfilaria into view

5- **Biochemical methods** (more sensitive than skin-snip microscopy)

- Skin-snip PCR
- ELIZA
- Enzyme immune assays (EIAS)
- Antigen detection
- Serum antibody test card using recombinant antigen to detect O.volvulus specific IgG4 in finger-prick whole blood specimens

- Triple antigen indirect ELISA rapid format card test
- Specific urine antigen dipstick test (highly sensitive and specific)

6- <u>High eosinophilia</u> (30%)

7- <u>Mazzotti test:</u>

- Used only for patients with repeated negative skin snips and normal eyes
- Useful to detect light infection but potentially dangerous
- Appearance of itching popular skin reaction within 24 h after an oral dose of DEC (6 mg), due to liberated protein of the dead microfilaria
- May be accompanied by fever, limb edema and even hypotension or worsening of eye damage

8- <u>DEC patch test</u>

- 1 cm^2 filter paper soaked in a solution of DEC is applied to the skin of the patient → if positive, this will provoke intense localized itching and inflammation at the site of application

Treatment

1- <u>DEC</u> → no longer recommended in the treatment of onchocerciasis

2- <u>Ivermectin</u>

- <u>Structure</u> → synthetic macrolide antibiotic
- <u>Dose</u>
  - 150 µg/kg orally in the morning on an empty stomach, repeated every 3-6 months when treating individual patients and at 1 or 2 year intervals when used in community control programs in Africa or the Americas, respectively
- <u>Mode of action</u>
  - It kills microfilaria by immobilizing them (neuromuscular paralysis), so they are carried away from their usual locations by lymphatics. Therefore in contrast to treatment with DEC, microfilaria death following Ivermectin is less immediate & is

less likely to provoke irreversible inflammatory responses in vulnerable organs such as the eye.

- Has little effect on adult worms other than reducing embryogenesis. Therefore, elimination depends on repeated doses over years → a conservative estimate is that annual treatment with ivermectin alone would need to be sustained for at least 14 yr to cover the estimated lifespan of the adult worm

- Pharmacokinetics
  - Peak level after 3 hr and half life 22 hr
  - It is microfilaricidal, effective in clearing microfilaria within 2 weeks, but may reappear by 3-6 months after treatment
- Indications
  - Onchocerciasis
  - Trichuriasis
  - Strongyloidiasis
  - Loiasis (after specific precautions)
  - Creeping eruptions "cutaneous larva migrans"
  - Filariasis
  - Scabies
- Contraindications
  - Pregnancy & lactation
  - Concomitant heavy Loa Loa infections → as fatal cases of encephalopathy have occurred
- Side effects → esp. occur in patients with greatest microfilaria
  - Mazzotti reactions are rare following treatment
  - However, temporary increase in itching, papular eruptions, limb edema, headache , fever and mild hypotension may sometimes occur
  - Myalgia, sore throat and cough
  - Lymph node tenderness & enlargement

- Ocular reaction less likely
- Ivermectin resistance → recent examples of persistent microfilaria despite multiple doses of ivermectin in Ghana (genetic heterogeneity of O.volvulus and pre-exist resistant alleles)

3- Doxycycline

- Dose → 100 mg orally daily for 6 weeks
- Mode of action
  - Kill the endosymbiotic Wolbachia organisms in filarial spp.
  - Effective in blocking embryogenesis and can maintain freedom from microfilariae up to 2 yrs
  - Has a limited microfilaricidal effect

4- Nodulectomy

- Was advised in the past for head nodules in an attempt to ↓ the risk of eye disease
- However, this not effective in eliminating the risk of eye disease; because not all nodules are necessary evident and remaining nodules would continue to produce microfilariae

5- Current regimen for treatment of individual patients

- Combination of doxycycline 100 mg daily for 6 weeks
- + a dose of ivermectin 150µg/kg on completion of the course of doxycycline (at week 6), and a further dose after 3-6 mo
- Unless contraindicated (age < 9 yr, pregnancy and breast feeding)

6- Chemotherapy for community control of onchocerciasis

- APOC → ivermectin 150 µg/kg once / year
- OEPA → ivermectin 150 µg/kg once / 2 years
- Timescales :
  - At least 25 yrs in areas of medium or high endemicity
  - > 35 yrs if there is heterogeneity in exposure to S. damnosum

- Significant reduction in these timescales may be possible with the development of short course antibiotics that targeting Wolbachia which can be safely administered to entire communities
- High risk foci of Loa loa are currently excluded from community ivermectin programmes; because of the risk of encephalopathy in individuals with high Loa microfilaraemias

FILARIASIS

Wuchereria bancrofti (Filariasis)

Pathogenesis

1- Infective stage → filariform larva → microfilaria

2- Definitive host → man

3- Habitat → lymph vessels and lymph nodes of the trunk, groin, scrotum, retroperitoneal tissues and limbs

4- I.H → Female night-biting Culex pipiens in Egypt considered the main vector in Nile delta (cyclodevelopmental transmission= no multiplication), some anopheles & aedes spp. In other location

5- Mode of infection → bite of infected mosquitoes (Transmission is less efficient compared to malaria as filariform larvae aren't injected directly into blood but deposited on the skin, then they actively invade the new host via the bitten area).

6- Nocturnal periodicity → microfilaria present in peripheral blood at night (between 10 pm, 2 am) and in the daytime hiding in the capillaries of the lung

7- Distribution

- W. bancrofti endemic in Africa
- In Egypt → It is endemic in Qalyubia (highly endemic), Sharkiya, Monufiya, Dakahkyia, Damietta & Giza. In contrast, filariasis appears to be absent in middle & upper Egypt except for a small hypo-endemic area in Asyut.

8- Pathological lesions:

- Are confined to the lymphatic system
- Related to adult worms (living or dead) but not to microfilariae
- Inflammatory phase due to mechanical irritation, toxins and 2ry bacterial infection
- Obstructive phase due to
    - Blockage of the lumen by worms

- Proliferation of the endothelial lining
- Fibrosis of lymph vessels and lymph nodes

- Obstruction of lymph flow → dilatation and varicosity of lymphatics

Clinical features

1- Incubation period → 8-16 months (may up to 15 yr)

2- Asymptomatic amicrofilaraemia

3- Asymptomatic microfilaraemia

4- Tropical pulmonary eosinophilia ®

5- Acute filarial fever without lymphadenitis:

- Acute episodes often recur several times a year
- Fever, headache and malaise that should be distinguished from other causes of fever in tropics.

6- Acute filarial lymphangitis (AFL):

- Occur following death of adult worm (spontaneously or post-treatment).
- Circumscribed inflammatory nodule or cord –streaks- with centrifugal lymphangitis (i.e. spreading away from the affected node)[signs of inflammation include redness, tenderness. Swelling, hotness]
- Usually mild & rarely results in lymphodema.
- Secondary bacterial infection & abscess formation in the affected node may occur in severe cases

7- Acute dermato-lymphangio-adenitis (ADLA):

- Intense local inflammation resembling cellulitis of erysipelas
- Secondary bacterial infection usually occur due to impaired lymphatic flow
- This result in diffuse SC inflammation which may be accompanied by ascending lymphangitis and is frequently associated with limb edema [acute episode of 1 week duration: high fever, pain, swelling, nausea and vomiting]
- Inflammation leads to damage of small lymphatic vessels & eventually fibrosis & progression to elephantiasis.

- ADLA is commoner than AFL in endemic regions & is more important as a cause of lymphodema and elephantiasis.

8- <u>Chronic phase:</u>

- Onset → May develops months or years after acute symptoms or without a history of acute disease
- The resultant lymphatic obstruction leads to lymphodema of the affected extremity & eventually to elephantiasis [excessive protein in lymph exudates stimulates proliferation of connective tissue → thickening of the affected part]
- Initially there is reversible pitting edema that gradually becomes non-pitting & permanent. The skin thickens and becomes dense (firm to hard) & nodular verrucose skin changes follows [the skin appears rough, folded, stretched and fissured]
- The most common sites affected include dependent parts → lower limb, scrotum, arms and breast
- Recurrent secondary bacterial skin infection, often streptococcal → may cause acute episodes of pain and fever & may be complicated by acute glomerulonephritis

9- <u>Other manifestations includes:</u>

- Hydrocele, usually unilateral (the commonest chronic manifestation of W. bancrofti filariasis)
- Lymph scrotum i.e. lymphatic fluid seeps through the scrotal skin
- Acute epididymitis and funiculitis (inflammation of spermatic cord)
- Monoarthritis
- Glomerulonephritis
- Chyluria → has a milky appearance, sometimes tinged pink because of the presence of RBCs which can be seen to sediment if the urine is left to stand in a conical jar
- Chylus ascites , chylothorax or chylocele due to rupture of dilated lymphatics

- Chylus diarrhea that may be complicated by malabsorption particularly of fat-soluble vitamins

Differential diagnosis

1- Filarial fever

- Malaria
- Acute bacterial lymphangitis
- Other acute or recurrent fevers

2- Groin swellings

- Hernias
- Hanging groin of onchocerciasis

3- Filarial lymph node enlargement

- Chronic infections
- HIV
- TB
- Lymphogranuloma inguinale
- Lymphoma and leukemia

4- Filarial orchitis, funiculitis or hydrocele

- Acute infections
- Brucellosis
- TB
- S. haematobium
- Surgical causes

5- Chyluria

- Other causes of lymphatic obstruction e.g. TB

6- Elephantiasis

- Chronic sidero- silicosis
- Milroy's syndrome
- Lepromatous leprosy
- Repeated streptococcal infection of the feet

Diagnosis

1- **Giemsa-stained thick blood films:**

- For microfilarial detection at the peak of microfilarial periodicity (i.e. 10 pm to 2 am for W. bancrofti).
- Relatively insensitive unless microfilaria is high (> 100mf/ml)
- Concentration techniques greatly improve sensitivity.

2- **DEC provocative test:**

- Used to induce parasitaemia during the day
- Single dose of DEC provoke microfilaremia then collection of peripheral blood after 30-60 minutes for staining & examination can occur
- Rarely used due to potential risk of Mazzotti reaction in patients coinfected with Onchocerciasis or potential risk of encephalopathy in patients coinfected with Loiasis
- ELISA (TropBio-test) & Rapid finger-prick immunochromatographic card test for detection of circulating W. bancrofti antigen
    - These tests are very sensitive, specific
    - Diagnose the adult worm infection as well as microfilaria at any time of the day, thus overcoming the problem of periodicity

3- **IgG4 tests**

- Bm 14 test for both W. bancrofti & Brugia malayi infections and Bm-RM test for B. malayi infection
- May be used for monitoring control programs and screening travelers

4- **PCR assays** → have been developed for W. bancrofti & B. malayi

5- **CBC** → eosinophilia common during the acute phase

6- Examination of the **chylous** exudates for microfilariae e.g. chyluria

7- **Scrotal U/S scanning:**

- May be useful for demonstrating live adult worms (the filarial dance sign) either for diagnostic purposes or for following up response to treatment

Treatment

1- **Diethylcarbamazine (DEC): [the mainstay]**

- Usual regimen
  - 6 mg/kg /day orally in 3 divided doses after meals for 10-14 days (with maximum total dose of 72 mg/kg = usually only for 12 days).
  - Starting by 1 mg/kg three times daily on days 1 and 2 to lessen side effects
  - May be repeated a month after completion of the initial course.
  - Must be combined with antihistaminics or corticosteroids → as rapid destruction of microfilariae and release of antigens may result in allergic reactions
- Effect
  - Effective for microfilaria but has limited effect in killing the adult worms
  - Microfilaria count falls within a month & remains low for 6-12 months.
- Contraindications
  - Should be avoided in areas endemic for Onchocerciasis or Loa Loa for fear of provoking Mazzotti reaction or encephalopathy

2- **Albendazole:**

- Kills microfilaria & has some effects on adult worms if taken for prolonged course

3- **Ivermectin:**

- Kills microfilaria but not adult worms.
- It's mainly used in combination with DEC or albendazole

4- **Doxycycline:**

- Dose: 100 mg twice daily for 6 weeks is highly effective
- Effect
  - 99% reduction in microfilaria at 12 months

- Addition of a single dose of ivermectin on completion of the course result in complete amicrofilaraemia

- Mode of action: it eliminates the microfilaria gradually, thus avoiding the adverse inflammatory events that may follow rapid destruction of parasites & release of bacterial symbionts, by the following actions:
  - It has been shown to kill the endosymbiotic Wolbachia organism in filarial species i.e. it eliminates Wolbachia surface protein (the inflammatory trigger for chronic disease).
  - It blocks embryogenesis & can maintain freedom from microfilaria for up to 2 years.
  - Its use in treatment of lymphatic filariasis has been shown to decrease plasma levels of lymphangiogenic factors, reduce dilatation of lymphatic vessels, improve lymphodema & reduce Hydrocele
- Adults are also gradually eliminated → avoiding the development of inflammatory nodules sometimes seen with rapid death of adult worms following treatment with DEC or ivermectin?
- Indications:
  - Onchocerciasis
  - Filariasis
  - Brucellosis
  - Rickettsial infection & Leptospirosis.
  - Malaria prophylaxis
- Contraindications:
  - Pregnancy, lactation
  - Children < 9 years
- Side effects:
  - Allergy, skin rash.
  - GIT upset; nausea, vomiting
  - Teeth discoloration & deformity due to binding with calcium

5- Treatment of individual patients:

- Coinfection with Onchocerciasis:
    - Doxycycline 100 mg twice daily for 6 weeks followed by oral dose of Ivermectin 150 µg/kg on completion of the doxycycline course
    - Further dose of Ivermectin 3-6 months after unless contraindicated
- Coinfection with Loiasis esp. with high microfilaraemia:
    - Albendazole 200 mg twice daily for 3 wks to gradually reduce the microfilaria followed by a course of DEC or Ivermectin
- Filariasis infection alone
    - Doxycycline 100 mg twice daily for 6 weeks followed by a dose of DEC 6 mg/kg on completion of the doxycycline course
    - Further dose of DEC 3-6 months after unless contraindicated.

6- Side effects of drugs in decreasing order of frequency:

- General reactions associated with intensity of microfilaraemia
    - Headache, fever, dizziness
    - Anorexia, malaise, nausea
    - Urticaria, vomiting and wheeze
- Local reactions
    - Scrotal nodules due to death of adult worm
    - Lymphadenitis, funiculitis, epididymitis
    - Lymphangitis, orchitis, abscess formation, ulceration
    - Rarely, transient lymphoedema

7- Prevention of morbidity

- Lymphoedema → elevation, massage, exercise and bandaging of the affected limb
- Prevention of 2ry bacterial infection → careful hygiene, use of disinfectant soap and water, early treatment of any wounds or abrasions, penicillin prophylaxis in recurrent streptococcal infections

- Chyluria → good nutrition and bed rest, surgery in some cases
- Hydrocele → surgery
- Surgical treatment of limb elephantiasis → unreliable, leaves scars and expensive

8- Control of Filariasis:

- Mosquito control:
  - Insecticide-impregnated mosquito nets
  - Animal barrier and control of mosquito breeding
- Mass treatment of at-risk populations:

  - **Outside Africa:** little risk of Onchocerciasis or Loiasis
    © A single dose of DEC 6 mg/kg annually together with a single dose of albendazole 400 mg
    © Annual treatment should continue for 20 years
  - **Within Africa:**
    © A single dose of Ivermectin 150-400 µg/kg annually together with a single dose of albendazole 400 mg
    © Annual treatment should continue for 30 years
    © Areas at high risk of Loiasis are currently excluded from Ivermectin programs (Central province of Cameroon is the main focus)

Brugian filariasis

Characters

1- It's caused by **Brugia malayi** in certain rural areas of Asia

2- **Mansonia species** of mosquito are the major vector although Anopheles may also be involved

3- Clinically:

- Brugian filariasis is less severe than bancroftian disease
- Elephantiasis is usually limited to below the knees and scrotal involvement is less common

Occult filariasis (Tropical pulmonary eosinophilia)

Pathogenesis

1- **Asthma-like syndrome** caused by hyperactive immunological response to human filaria usually Wuchereria bancrofti or Brugia malayi

2- Microfilariae are destroyed in pulmonary capillaries and antigen release recruits large numbers of **eosinophils t**hat release major basic protein and other chemicals

3- **Granulomatous reaction** may eventually progress to fibrosis & permanent pulmonary damage, possibly due to antigenic similarity between the filarial worm enzymes and proteins found on human pulmonary epithelium

Clinical features

1- Commonly found in India and in parts of West Africa [Aedes mosquito]

2- It usually occurs among children & young adults

3- Short history of cough, dyspnea, wheezes:

- That worsens at night
- Often preceded or accompanied by low grade fever and malaise

4- Chest exam. → **asthma like**

5- Lymphadenopathy or splenomegaly sometimes present

6- Rarely **7th nerve palsy or focal neurological signs**

Diagnosis

1- **Blood tests**

- Marked eosinophilia → usually > 3x 10^9/L or much higher
- ESR → ↑
- IgE → markedly increased
- Tests for filarial antibodies → show high titres
- Filarial antigen tests → positive
- Microfilariae can't usually be found in peripheral blood, even by sensitive filtration methods

2- **High eosinophilia with high filarial antibody titres & response to treatment** are the bases for diagnosis

3- **Chest X-ray**

- May be normal
- Often shows → diffuse alveolar mottling with small 1-2 mm nodules in the middle and lower zones
- Sometimes → Hilar adenopathy
- Less often → pleural effusion or areas of hyperacute pneumonitis

4- **Pulmonary function tests**

- Restrictive changes & poor gas diffusion
- Obstructive changes are less common

Differential diagnosis

1- Migrating helminthes, esp. Ascaris in children
2- Strongyloides stercoralis or hookworms [temporary disability]
3- Severe allergic asthma
4- Bronchopulmonary aspergillosis

Treatment

1- May remit **spontaneously** and recurs following treatment in 20% of cases
2- **DEC** → 6 mg/kg in divided doses for 12-21 days is the standard treatment
3- **If no adequate response** → a second course of DEC is started with addition of albendazole 400 mg twice daily for 3 weeks
4- Symptomatic response usually within days but lung function can remain impaired for months
5- **Symptomatic treatment** → Bronchodilators, corticosteroids or antihistaminics

Loiasis (Eye worm)

Pathogenesis

1- Cause → Loa loa

2- Infective stage → filariform larvae → microfilaria

3- Definitive host → man

4- Habitat → SC tissues free migrating, may seen under the conjunctiva

5- I.H → Chrysops (red day biting insect- deer flies)

6- Mode of infection → bite of infected mosquito (as W.bancrofti)

7- The microfilaria has blood diurnal periodicity

8- Pathology due to adult worms

9- Distribution → tropical forests of Africa

Clinical features

1- Urticaria, itching & creeping sensation → due to migration of adult worms

2- Arthralgia and malaise

3- **Calabar "fugitive" swelling:**

- Transient subcutaneous fugitive swelling (SC edema) in the size of hen's egg
- Localized, hard and non-pitting
- Painless, but itchy
- It appears abruptly & disappears gradually without suppuration after 2-3 days
- Cause → allergic reaction to the worm metabolites inside which the adult worm may or may not be present, it is provoked by trauma to the migrating adult worm and local pain
- It may be found anywhere but it's commonly found in extremities esp. upper limb
- It occurs as early as 3 weeks after infection

4- Eye affection:

- Adult worm may be seen in the conjunctiva (subconjunctival migration) or eye lids
- If local anaesthetic and surgical instruments are available, the worm can be removed from the eye
- It causes intense pain, inflammation, irritation and lacrimation
- It doesn't cause blindness

5- Complications

- Ocular:
    - Retinal hemorrhage (with encephalitic manifestations)
    - Recurrent chorio-retinitis
- Encephalitic syndrome:
    - Potentially fatal meningio-encephalitis following inappropriate treatment of patients with high microfilarial load by Diethylcarbamazine **(DEC)** due to sudden release of microfilarial proteins into blood stream (Herxheimer reaction) → capillary damage of brain meninges
- Polyarthritis:
    - Acute inflammation of ankle & knee with PMNLs and microfilaria in the joint fluid
    - It responds to treatment with DEC
- Proteinuria is relatively common and hematuria may occur
- Pulmonary infiltrates and pleural effusion may occur
- Lymphangitis and hydrocele may occur
- Endomyocardial fibrosis:
    - It's supposed to be due to allergic heart disease & hypereosinophilia
    - It account for 10-15% of heart diseases in area where Loa Loa occurs

Diagnosis

1- **Thick blood films during the day 10 am to 2 pm**
   - Giemsa or Wright stains → detect microfilaria (concentration techniques may be helpful if films are negative).

2- **Quantitative microfilarial load**
   - Useful in predicting the likelihood of an adverse reaction to treatment
   - Probable cases of Loa-related encephalopathy → > 10,000 Mf/ml before ivermectin treatment & > 1000 Mf/ml after treatment
   - Patients with pretreatment microfilarial load > 30.000 Mf/ml are at greatest risk of encephalopathy
   - However, caution is advised in all patients with pretreatment microfilarial load > 2500 Mf/ml, as serious adverse effects may occur at lower levels

3- **Adult worm** may be removed from eye or skin

4- **Serology:** ELISA may be helpful in diagnosis of travelers from endemic areas but lack specificity as cross react with other filarial parasites & Strongyloides spp occur

5- **X-ray** → incidental findings of dead calcified worms

Treatment

1- **Pretreatment precautions:**
   - Caution is advised in all patients with pretreatment microfilarial load > 2500 Mf/ml → because massive release of antigens from dying microfilariae may precipitate meningoencephalitis or renal failure
   - Albendazole 200 mg twice daily for 3 wks → to gradually reduce the microfilaraemia followed by a course of DEC or Ivermectin
   - Prednisolone 20 mg/day for 3 days before and for 3 days following the start of antihelminthic treatment → may reduce the risk of encephalopathy
   - In the past → plasmapheresis has been used to reduce heavy microfilarial loads prior to treatment under steroid cover

2- **Antihelminthic course:**

- Diethylcarbamazine (DEC):
  - 6 mg/kg/day orally in three divided doses for 7-10 days
  - Repeated every 2-3 months if symptoms remain
  - It affects both adult worms & microfilaria
- Ivermectin:
  - 150 µg/kg single oral dose prior to treatment with DEC reduces the likelihood of Mazzotti reaction in patients coinfected with Onchocerciasis

Trichinella spiralis

Pathogenesis

1- Infective stage → encysted larvae in muscles

2- Definitive host → rat, pig and man

3- Habitat → small intestine

4- I.H → rat, pig and man

5- Mode of infection → ingestion of raw or undercooked pork meat (or canned minced meat) containing the encysted larvae which is resistant to heat below boiling point

6- In the intestine → larvae → adults → larvae invade deep in the mucosa (1st week) → deposited directly into lymphatics & carried to various organs -2nd week- (commonly skeletal muscles where they become encapsulated – 3rd week- → local myositis).

7- Sites

- Skeletal muscles: tongue, deltoid, biceps, gastrocnemius, intercostals & muscles of neck & eye
- Heart: in which larva doesn't become encapsulated

Clinical features

1- In the 1st week after meal → nausa, vomiting, colic and diarrhea

2- **Fever**

3- **Edema of eyelids** is the most constant & is often the earliest sign

4- **Muscle** pains, tenderness and weakness of affected muscles (local myositis)

- Difficulty in eye movement, mastication, breathing and speaking

5- **Cardiac affection:**

- Myocarditis
  - Cause → local infiltration of lymphocytes & eosinophils and interstitial edema
  - Leads to dilatation of the heart, arrhythmia and sudden death in about 5% of cases
- Pericarditis
- Chest pain in 2nd or 3rd week and congestive heart failure may follow
- Recovery expected with treatment

6- **In the 3rd week** → encystation only in striated muscles → rapid recovery, but in severe cases → severe toxaemia → myocarditis, pneumonia or encephalitis

Diagnosis

1- **Trichinoscopy:** muscle biopsy (of deltoid, biceps or gastrocnemius):

- Small samples of infected muscles are taken, and examined for larvae
- Larvae can be seen in specimen either by compression between 2 slides or after digestion in gastric juice (acid pepsin) and concentration by centrifugation

2- **X-ray for muscles** → small calcified cysts (rarely recognizable)

3- **Serological** → ELISA for larval antigens

4- **CBC** → high eosinophilia (20-50%)

5- **Stool analysis** → rarely larva or adult

6- **ID test (Bachman test)** → injection of 0.1 cc of 1:10,000 dilution of antigen prepared from dried powdered larvae leads to local wheal in +ve cases in 20 min

7- **Xenodiagnosis** → rat fed on infected pork

Treatment

1- **Albendazole** 400 mg twice a day for 8–14 days. Or

2- **Mebendazole** 200–400 mg three times a day for 3 days

3- **Bed rest** is important

4- **Analgesics and/or antipyretics** → for muscle pains, headache and fever

5- **Corticosteroids** → may be life-saving in severe case to control allergy and ↓ inflammation

Dracunculus medinensis (Medina or Guinea worm)

Pathogenesis

1- Infective stage → larvae after 3 weeks in Cyclops

2- Definitive host → man, dog, horse, cattle and monkey

3- Habitat → the gravid females migrate in SC tissues in parts that contact water (feet, legs, shoulders and back)

4- I.H → Cyclops (water flea)

5- Mode of infection → ingestion of well water contaminated with Cyclops infected with larva of Medina worm (gravid females appear in SC tissues 12 months later)

6- The gravid female migrates from retroperitoneal space to the lower limbs where it creates an irritant itchy blister

7- When patients wash his leg in water the blister ruptures & the uterus of worm discharge thousands of comma shaped larvae into water

8- Distribution → areas where step wells are common (now confined to a few African countries)

Clinical features

1- **Usually seasonal** (often most frequent in the height of the dry season when water is scarce)

2- **When worms emerge through the skin**

- Burning pain that motivates patients to immerse the limb in water → encouraging transmission

- Allergic responses may occur esp. after immersion in water→ including urticaria or even asthma

3- **Itchy blisters: (main presentation)**
   - Begins as red papule → vesicle
   - Site: at the point of emergence (anterior end of the worm) → usually, on the foot or lower leg but sometimes, the arm, scrotum or any part of the body
4- **Secondary bacterial infection** (abscess formation is common) or ulceration of the blister
5- **Arthritis** with effusion, sometimes occur due to wandering adult worm
6- Rarely, **vertebral disc prolapse or paraplegia** due to wandering adult worm

Diagnosis is essentially clinical

1- Examination of milky discharge released from the ulcerated blister after immersion in water → **comma shaped larva**.
2- The adult may be protruded from the blister and when immersed in water → **white cloud of larvae (characteristic)**
3- **X-ray** → dead calcified long worm may be seen
4- **CBC** → high eosinophilia

Treatment

1- **No specific drugs**
2- **Albendazole or metronidazole** courses to reduce inflammatory response and edema, but of marginal benefit [no effect on adult worms or larvae – spontaneous elimination or removal only]
3- **Mechanical removal** of worms using gradual traction by rolling it around a stick
4- **Surgical removal** of the worm before it emerges, by extraction through small transverse incisions → ↓ the risk of infection and disability
5- **If the uterus has emerged**
   - Discharge the larvae by immersion in water and take care to dispose of the water hygienically

- The traditional method is to tie the end of the emerging worm out slowly over many days, taking care not to rupture the worm

6- **Ulceration** → antiseptic dressings

7- **For 2ry infection** → antibiotics

8- **For allergic reactions** → antihistaminics and corticosteroids

9- **Tetanus immunization** → should be checked and updated if necessary

Strongyloides

Pathogenesis

1- Infective stage → non sheathed filariform larva

2- Definitive host → man

3- Habitat → small intestine

4- I.H → no (soil)

5- Mode of infection

- Penetration of intact skin or mm of the mouth by filariform larvae contaminated in soil
- Autoinfection → some rhabditiform larvae while passing down in the lumen of intestine moult twice into infective filariform larvae → ↑ worm burden → persistent infection
    - Internal autoinfection : the filariform larvae penetrate the intestinal mucosa
    - External autoinfection : the filariform larvae penetrate the perianal skin and repeat the cycle
- Sometimes, through ingestion of contaminated food or water

6- Rhabditiform larvae not the eggs are found in human feces

7- It is a facultative parasite having a parasitic form in the mm of small intestine and a free living form in the soil [the only common soil-transmitted helminth infecting human in which the worms can multiply in the free living stage]

8- Not regarded as a classical HIV associated infection

9- There is a well established association with HTLV-1 infection

10- S. fulleborni → a related worm which reported to infect children, and associated with a condition known as "swollen belly syndrome" in younger children in Papua New Guinea

Clinical features

1- Asymptomatic → in many infections

2- Acute infection

- Itchy eruption at the site of penetration (patient seldom recollect this)
- Cough and wheeze because migration of the larvae in the lung- Loffler's syndrome- (also uncommon) ® , X-ray shows shadows in the lung similar to those of tropical eosinophilia
- Vague and ill defined epigastric pain and tenderness (duodenitis), may simulate duodenal ulcer
- Watery mucus diarrhea which can be marked associated with constipation (Cochin-China diarrhea), steatorrhoea occasionally and even bloody diarrhea
- Weight loss (usually associated with diarrhea)

3- Chronic strongyloidiasis

- Larva currens or racing larva (creeping eruption)
  - Pathognomonic skin eruption
  - Caused by the migration of larvae through the skin during external autoinfection
  - Serpiginous wheal (a raised line) surrounded by a flare
  - Evanescent (comes and goes in a few hours) and travel rapidly
  - Very itchy
  - Confined to the trunk between the neck and the knees (starts in the perianal region and extends across the buttocks, thighs and the back)
- Intestinal symptoms
  - Vague irregular bouts of looseness of the stools

- Diarrhea is not constant
- Bloody diarrhea not a feature of uncomplicated chronic cases
- Sprue-like syndrome of diarrhea and weight loss may occur

4- **Hyperinfection syndrome** → (opportunistic parasite) ® see below

Diagnosis

1- **Clinical diagnosis**

- High eosinophilia + unexplained diarrhea + typical larva currens rash → are all highly suggestive in at-risk subjects
- In such cases, and even with –ve parasitology → a therapeutic trial should be started [despite all diagnostic methods, diagnosis may remain in doubt]

2- **Stool examination** → Detect rhabditiform larvae

- Simple smear and concentration
  - May be negative in acute infection (larvae are easy to detect – frequently scant and appear frequently- in hyperinfection and in chronic cases)
  - There are well documented cases with up to 12 consecutive stool samples although subsequently shown to have strongyloidiasis
- Stool culture with charcoal

3- **Duodenal aspirates** by flexible gastroduodenoscopy or Enterotest capsule (hairy string test) are options→ microscopy shows the larvae

4- **Small bowel biopsy** → atrophy of the villi and presence of the larvae

5- **Serological tests**: e.g. ELIZA

6- **Marked ↑ of IgE and eosinophils** → acute infection (in chronic form, these are less constant & in hyperinfection, there is no eosinophilia)

Treatment

1- **Ivermectin**

- The most effective therapy
- Dose → 200 µg/kg/day for 3 days
- Although, single doses of 6 mg/day for 3 days have been effective

- Also, single 1-day dose may be effective
- In hyperinfection syndrome → SC injection of 12 mg of ivermectin as a single dose may be successful (veterinary one case study)

2- <u>Albendazole</u>

- Dose → 400 mg/day for 3 days in acute infection & for 7 days in chronic cases
- A dose of 400 mg twice daily is more effective

3- <u>Thiabendazole</u>

- Less effective with more common side effects (nausea, vomiting, dizziness and occasional neuropsychiatric problems)
- Dose → 25 mg/kg twice daily for 3 days (usually 1.5 g twice daily)
- It does not kill larva or ova, so treatment should be repeated after 2 weeks to overcome relapse

4- <u>Corticosteroids are contraindicated</u>

5- <u>Treatment of immunodeficiency problem</u> that encouraged this opportunistic parasite

Hyperinfection syndrome

Definition

1- A rare complication of S. stercoralis infection usually **<u>the chronic form</u>** of the disease

2- <u>Occurs when host immunity</u> is significantly and usually **<u>abruptly reduced</u>** [the parasite produces massive number of rhabditiform larvae with rapid and disseminated migration into tissues not involved in the normal human life cycle]

Risk factors

1- <u>Systemic steroid treatment</u>

- The most common cause
- A well reported scenario for hyperinfection is post-renal transplant

2- <u>Other Immunosuppressives treatment</u>

3- Leukemia & lymphoma

4- Post-irradiation treatment

5- Severe malnutrition

6- Diabetic ketoacidosis

7- Lepromatous leprosy

Clinical features

1- Severe and often bloody **diarrhea**

2- **Bowel** inflammation with multiple microperforations

3- Bacterial **peritonitis** and paralytic ileus

4- Gram-negative **septicemia**

5- **Pulmonary** exudates, hemoptysis, pleural effusion and hypoxia

6- **Encephalitis** , bacterial meningitis, brain abscess or infarction

7- Hypoproteinaemia and **malabsorption**

Diagnosis [essentially clinical & a high index of suspicion is needed]

1- Usually **No** eosinophilia

2- **Larva** is usually easy to find in stool & other body fluids (e.g. peritoneal and/or pleural exudates, bronchoalveolar lavage samples).

Treatment [outcome is poor]

1- **Specific** → as strongyloides ®

2- **Supportive therapy** → fluids & antibiotics

3- **Prevention**

- Regular diagnostic screening for strongyloidiasis and eradication of the disease if found for patients in endemic areas needing immunosuppress e.g. steroids in severe asthmatics
- Like strongyloidiasis, TB and amoebiasis should also be screened

Enterobiasis

Pathogenesis

1- **Infective stage** → mature eggs

2- Definitive host → man

3- Habitat → Caecum, appendix and adjacent parts of the small & large intestine

4- I.H. → no (eggs directly infective)

5- **Mode of infection**

- Autoinfection: movement of females at time of egg deposition → intense irritation and itching at the anus (about 10,000 ova) → eggs carried under finger nails to reach the mouth (in 30% of cases , eggs found beneath nails)
- Contaminated food and drink
- Direct contact with patients (hand to hand) or indirect contact by handling contaminated articles, clothes, bed linens and toilet seats
- Air born infection: eggs carried by air currents from exposed bed sheets and blankets then inhaled and swallowed
- Retroinfection: eggs hatch in the perianal region and larvae migrate back into the rectum and large intestine

Clinical features

1- **Pruritus ani especially at night**

- Due to egg laying in the perianal skin

2- Nervous irritability, hyperactivity and insomnia

3- 2ry bacterial infection and perianal eczema may occur

4- **Secondary enuresis** → due to irritation of urethra and urinary infection

5- **Migration of females to ectopic sites** stimulates granuloma formation:

- Migration to the vulva and vagina → vulvovaginitis (itching), vaginal discharge, they may migrate to the uterus or fallopian tubes
- Migration to the urinary tract → infection and enuresis
- Migration to the appendix → appendicitis

- Migration to the intestine → diarrhea and abdominal pain
- Migration to the peritoneal cavity through uterine tubes → pelvic peritonitis

Diagnosis

1- Clinical

- Usually children with pruritus ani at night

2- Laboratory

- Detection of adult worms in the stool or perianal region
- Detection of eggs in
    - Stools → by direct smear and conc. (rarely +ve < 5% of cases)
    - Perianal region → by swabs (should be taken in the morning immediately after the patient's wakes up i.e. before defecation or bathing)
    - N.I.H. swab: the perianal region is swabbed with a piece of non adhesive cellophane paper to which the eggs adhere
    - Scotch adhesive tape swab: a piece is applied to the perianal skin with its sticky surface thus the eggs are transferred to the tape which is then spread on a slide and examined. A drop of tulouene or xylene is put on the slide before the tape to clear the epithelial cells and debris facilitating search for eggs (this method gives the highest % of +ve results and the greatest number of ova)

Treatment

1- Mass treatment: All family members should be simultaneously treated even asymptomatic subjects to prevent reinfection

2- Albendazole

- Single oral dose of 400 mg
- It should be repeated after 2 weeks to eliminate any infection acquired from ingestion of eggs that remain in the environment following the 1st dose (eggs remain viable 2 weeks) [the 2nd dose expels worms while still immature]

3- Mebendazole

- Single oral dose of 100 mg, repeated after 2 weeks

4- Local treatment

- Application of white oxide of mercury (white precipitate ointment) around the anus at night → relieves itching, kills females that come out to deposit eggs and prevents dispersal of eggs

5- General measures

- Self cleanliness
  - Cutting finger nails short
  - Wash hands with scrubbing the nails especially before eating and after defecation
- Boiling of underwear and bed sheets
- Toilet seats must be washed frequently with disinfectants
- Infected children should use tightly fitting trousers at night to prevent autoinfection
- Protection of food and drink from contamination

Trichostrongylus colubriformis

Pathogenesis

1- Infective stage → ensheated filariform larva

2- Definitive host → Herbivorous animals (sheep, goats, camels) and occasionally man

3- Habitat → small intestine (jejunum) and may invade the biliary passages

4- I.H. → no (soil)

5- Mode of infection

- **Ingestion** of filariform larvae with contaminated food (green raw vegetables) and water
- لا تخرم الجلد ولا تذهب للرئة

Clinical features

1- Light infection → no symptoms

2- **Heavy infection**

- Intestinal irritation: colic, diarrhea,..
- Hypochromic microcytic anemia
    - Hemorrhage at sites of attachment
    - Sucking of blood (worms insert their anterior ends into the mm under the epithelium)
- May be signs of cholecystitis

Diagnosis

1- Detection of **eggs** in stool (smear and conc.) or duodenal aspirate

2- Stool culture may show **larvae**

Treatment

1- **Thiabendazole**

- 25 mg/kg twice daily for 2-3 days

Capillaria philippinensis

Pathogenesis

1- Infective stage → capillaria larvae in small fishes intestine

2- Definitive host → fish eating birds and occasionally man

3- Habitat → small intestine (mucosa, lumen of jejunum) [adults, eggs, larvae]

4- I.H. → fresh or brackish water small fishes

5- **Mode of infection**

- Ingestion of raw or undercooked whole fresh or brackish water fishes (small fish are difficult to eviscerate so they are eaten as a whole)
- Internal autoinfection

6- **Pathology**

- The pathological process occurs mainly in the mucosa of the jejunum
- In severe infection, the crypts are usually atrophic and infiltrated with inflammatory cells → malabsorption syndrome → pathological changes in other organs

Clinical features

1- **Abdominal gurgling** (borbor gygmi) → 1st sign

2- Intermittent colic

3- **Chronic diarrhea** and vomiting

4- Loss of weight, marked weakness, dehydration and low grade fever

5- **Later**

- LL edema (hypoproteinemia)
- Signs of vitamins deficiency

6- **Death** may occur due to

- Severe electrolyte disturbances or
- Superimposed bacterial infection

Diagnosis

1- **Stool examination**

- All stages (thick shelled eggs, larvae and adults) are discovered in watery stool with a lot of Charcot Leyden crystals

2- **May be**

- Low serum proteins especially albumin
- Low serum Na, K and Ca

Treatment

1- **Specific**

- Mebendazole → 200 mg twice daily orally for 28 days or
- Albendazole → 200 mg twice daily for 10 days

2- **Supportive**

- Fluid and electrolyte replacement
- High protein diet and vitamins

Capillaria hepatica (rare)

- Diagnosis made by liver biopsy which shows trichuris like ova encapsulated in the liver
- Characterized by tender hepatomegaly + eosinophilia

Lung flukes

Definition

1- Lung flukes of the genus Paragonimus are zoonoses, but human infection can cause a **chronic cough with haemoptysis** which can easily be mistaken for TB

2- The most common cause of human disease is → **Paragonimus westermani**

Pathogenesis

1- Infective stage → encysted metacercaria in crabs, crayfish or shrimps (2nd I.H.)

2- Definitive host → man, dog, cat and pig

3- Habitat → cystic cavities in lung tissue and bronchi

4- I.H → 1st fresh water snail (Melania), 2nd crabs and crayfish

5- Mode of infection → ingestion of undercooked crabs, crayfish or shrimps

6- Distribution → Asia esp. Korea and China, rarely India, west Africa, South and central America

Clinical features

1- Acute infection

- Incubation period → few days to weeks
- Malaise, shivers, sweats
- Urticarial skin rash
- Abdominal pain

2- Lung disease

- Chronic productive cough
- Brownish red sputum, sometimes stained with blood (endemic haemoptysis)
- Occasionally, dyspnea or chest pain
- Complications → pleural effusions or empyema

3- Ectopic disease [migration from the gut]

- Abdominal pain and inflammatory masses
- Convulsions
- Cerebral tumor like presentations

- Mental disturbance
- Migrating SC lumps (larva migrans)
- Occasionally → diarrhea ± HSM

Diagnosis

1- **Sputum Or stool analysis** → characteristic operculated ova
   - Concentrate stool or mucoid sputum
   - Examine sputum for brownish flecks that may contain nests of eggs
2- **Bronchoalveolar lavage** → show eggs
3- **Serological diagnosis**
   - EIA or dot enzyme immunoassay using antigen from flukes or metacercariae is available in some endemic areas
4- **Eosinophilia** → in early disease
5- **X-ray chest**
   - Usually peripheral nodules or ring shadows (small cavities like clusters of graps)
   - Sometimes, there is a crescentic shadow of a fluke within the ring
6- **CT scan** is useful

Treatment

1- **Praziquantel** → highly effective
   - Dose : 75 mg/kg/day in three divided doses for 2 days or a single dose of 40 mg/kg
2- **Triclabendazole** → an alternative
   - Dose: 10 mg/kg once or on two successive days
3- **Treat cautiously** → if cerebral disease is suspected, as a sudden increase in intracranial pressure is possible [use dexamethasone to control cerebral edema]

Liver flukes

Causes

1- **Fascioliasis or liver rot**
   - Fasciola hepatica
   - Fasciola gigantica

2- **Oriental liver flukes**
   - Opisthorchis sinensis
   - Opisthorchis viverrini
   - Opisthorchis felineus

Fascioliasis

Pathogenesis

1- Infective stage → encysted metacercaria on aquativ vegetation or water

2- Definitive host → herbivorous animals (sheep, cattle and goats), occasionally man

3- I.H.
   - Lymnaea cailliaudi snail → F. gigantica
   - Lymnaea truncatula → F. hepatica

4- Habitat → bile duct and gallbldder

5- Mode of infection → ingestion of encysted metacercaria on aquatic vegetation (e.g watercress) or in contaminated water

6- Distribution → present in Egypt, esp. Alxandria and Kalioubya

7- Inflammation of bile ducts → fibrosis, thickening and expansion

8- The worm can synthesize and release large amounts of proline which is the mediator of hyperplastic response

Clinical features

1- Incubation period → 6-12 weeks

2- **Acute symptoms [due to migration]**

- Fever, malaise, abdominal pain and weight loss
- Urticaria
- Respiratory symptoms
- Tender hepatomegaly, may be evident
- Ectopic fascioliasis
    - During migratory phase → GIT lesions are the most frequent (in the serosa of the stomach, pancreas or may form a caecal mass)
    - Immature worms may enter the blood → Can cause granuloma or abscess formation in various organs or Migrating erythematous cutaneous nodules (cutaneous LM)

3- <u>At reaching the bile ducts</u>

- Symptoms usually subside spontaneously
- Anemia and pallor → due to blood loss into the bile in heavy infection

4- <u>Chronic symptoms</u>

- Recurrent cholangitis, cholecystitis, cholelithiasis or intermittent biliary obstruction (obstructive jaundice) → in minority
- Fatigue → may persist > 10 yrs
- May be hepatomegaly

Investigations

1- <u>Clinical</u>

- Fever + hepatomegaly + high eosinophilia → highly suggestive

2- <u>Laboratory</u>

- <u>Stool examination or bile aspirate microscopy</u>
    - Detect eggs in established infections (note that eggs appear in stools after 3 mo of infection)
    - Concentration techniques bay be required
- <u>High eosinophilia</u> is common and anemia
- ALT, AST → may be mild elevation
- <u>Serology</u> e.g. ELISA
    - Useful when eggs still unlikely present in stools

- Blood spots → can be collected on filter paper for later serological testing in large scale surveys

- Fasciola excretory-secretory antigen detection in faeces → useful both in prepatent and patent infections

3- Imaging

- U/S → usually normal (sometimes, demonstrate the living worm and its motility within the bile ducts or gallbladder
- CT with contrast → peripheral branched hypodense hepatic lesions (relatively specific for fascioliasis)
- ERCP → may show the tip of the worm protruding from the common bile duct and may be even extracted through endoscopy

Treatment

1- Triclabendazole [drug of choice][fasinex]

- Structure → new benzimidazole
- Dose
  - 10 mg/kg as single dose taken with food
  - Repeated after 12 hr in severe infections
- Side effects
  - Biliary colic, associated with the expulsion of dead or damaged parasites , commonly occurs 3-7 days after treatment → responds well to antispasmodics
  - There are reported cases resistant to triclabendazole

2- Nitazoxanide → 500 mg / 12 hr for 7 days is effective

3- Bithionol [the preferred treatment previously]

- Dose → 30 -50 mg/kg/day in three divided doses on alternate days for 10-15 days
- Side effects → pruritus, leucopenia and mild GI upset

4- In contrast to other fluke infections, **praziquantel is not effective** in treatment of fascioliasis

Halzoun (Parasitic pharyngitis)

Causes

1- **Eating raw liver**

- Of sheep and goats containing living fasciola
- In some regions as Syria and Lebanon
- The worm may get fixed to the mm of the pharynx → parasitic pharyngitis with inflammation, edema, dysphagia, dyspnea or even suffocation

2- **Linguatula serrata**

- Adults live in nose of dogs → eggs discharged with the nasal secretion → ingested by I.H (sheep and goats) → the larvae hatch in the intestine and migrate to the viscera and develop into nymphs
- When man ingests raw organs of these animals → the nymph may be fixed to mm of the pharynx → parasitic pharyngitis with inflammation, edema, sneezing, cough and vomiting

Treatment

1- Gargling with strong alcoholic drink

2- Emetics to induce vomiting

3- Tracheostomy with laryngeal obstruction

سؤال: لو أكلت كبده نية بها دودة أو بيض الفاشيولا ماذا يحدث؟

لا يحث فاشيوليزيز لأن العدوى تحدث عن طريق الميتاسيركاريا فقط الوحيد اللى يستطيع أن يقاوم الحامض المعدى , انما يحدث حالزون أو البيض ينزل فى البراز ويلغبط

Oriental liver flukes

Pathogenesis

1- Causes

- Opisthorchis sinensis → China and south east Asia
- Opisthorchis viverrini → China and south east Asia
- Opisthorchis felineus → eastern Europe and Russia

2- Infective stage → encysted metacercaria in fresh water fish

3- Definitive host → man and fish eating mammals (cat and dog)

4- I.H → 1st Bythrynia snail, 2nd fresh water fish

5- Habitat → bile duct, gallbladder and occasionally the pancreas

6- Mode of infection → ingestion of raw or undercooked infected fish or ingestion of metacercariae contaminating cooking surfaces and utensils

Clinical features

1- Asymptomatic → in most infections

2- Picture similar to **Katayama fever** may be present ®

3- **Vague abdominal pain**

- Site → right upper quadrant
- Typically in the late afternoon and lasts a few hrs
- Actually complain of feeling something moving about the liver

4- Lassitude, anorexia, flatulence, diarrhea and fever

5- **Hepatomegaly and jaundice** may be evident [cyst like cavities in the biliary tract and liver develop, the liver enlarges and becomes fibrotic]

6- **Malnutrition** and deficient fat soluble vitamins may be present

7- **Complications**

- Recurrent bouts of ascending cholangitis, jaundice and pancreatitis
- Biliary cirrhosis
- Cholangiocarcinoma → rarely in chronic infection due to adenomatous hyperplasia of the bile duct epithelium [adenocarcinoma]

- CCC associated with O. viverrini, is the most common form of liver cancer in Thailand (70% of the population are infected)
- CCC associated with O. sinensis, account for 15% of all 1ry liver cancers in Hong Kong
- Genitic factors, dietary nitrosamines and aflatoxins have been implicated in the development of this malignancy

Investigations

1- **Examination of stool or biliary aspirate**
   - Detect characteristic eggs
   - Concentration technique may be required

2- **Leucocytosis with eosinophilia**

3- **Serology** e.g. CFT is positive

4- **Coproantigen test** is now available for O. viverrini

5- **U/S** → may reveal gallstones and abnormalities of the biliary tract

6- **ERCP** is useful

Treatment

1- **Praziquantel** [effective]
   - Dose → 40 mg/kg in a single dose or
   - 25 mg/kg three times in 24 h after meals
   - In heavy infection → 3 day course should be used

2- **Annual praziquantel** → can dramatically reduce the prevalence of infection

Intestinal flukes

Causes

1- Fasciolopsis buski [the most common]

2- Echinostome

3- Heterophyes heterophyes

Fasciolopsis buski

Pathogenesis

1- Infective stage → encysted metacercaria attached to edible water plants, such as the water caltrop and chestnuct

2- Definitive host → man and pig

3- I.H. → 2nd planorbis snail

4- Habitat → small intestine esp. duodenum

5- Mode of infection → ingestion of edible water plants contaminated by encysted metacercaria

6- Distribution → from India to south east Asia esp. in pig- rearing communities

Clinical features

1- Asymptomatic in most infections

2- Most severe in children

3- Epigastric pain, vomiting and **diarrhea**, initially alternating with constipation but later becoming persistent [inflammation and ulceration of mucosa]

4- In severe infection (1000-2000 flukes) → diarrhea may be severe with intestinal **hemorrhage** and perforated intoxication [cause of death]

5- In severe cases → **malabsorption**, wasting, edema of the face and lower limbs and ascites

Investigations

1- Detection of characteristic **eggs in faeces** (smear&conc.)

2- Sometimes, adult flukes can be detected in faeces or vomitus

Treatment → praziquantel as before

Echinostome spp. → symptoms and treatment as F. buski

Heterophyes heterophyes

Pathogenesis

1- Infective stage → encysted metacercaria in fish muscles

2- Definitive host → man, dog, cat, fish eating animals

3- I.H. → 1st pirenella conica snail, 2nd brachish water fishes e.g. Filapa nilotica (bolty) and Mugil cephalus (boury)

4- Habitat → Small intestine

5- Mode of infection → eating fishes either raw, improperly cooked or freshly salted (< 10 days)

6- Distribution → common in Egypt in demietta and borollos esp. between fishermen

Clinical features

1- **Mild GI symptoms than F. buski** → abdominal colics, diarrhea with mucus and blood

2- **Ectopic eggs**

- CNS → space-occupying lesion and hemorrhage
- Heart → myocarditis or valve damage

Investigations and treatment → eggs + praziquantel as before

Schistosomiasis

Pathology

1- **Stage of invasion:** it results from penetration of human skin by cercaria leading to:
   - Cercarial dermatitis.
   - Cercarial pneumonitis

2- **Stage of ova deposition & granuloma formation:** The ova get deposited in the submucosa and become surrounded by granulomatous reaction in:
   - Urinary system (ureter, urinary bladder, seminal vesicles and prostate in case of S. hematobium infection).
   - The large intestine (the descending colon and the rectum in case of S. mansoni).
     - The characteristic bilharzial granuloma is formed of ova surrounded by epithelioid cells, eosinophils, lymphocytes, giant cells surrounded later by loose fibrous tissue.
     - As the worm begins to lay eggs, soluble antigen leaks out of the eggs and enters into the circulation → Ag-Ab complex formation and development of generalized immune complex disease.
     - The immune complex disease theory probably explains why acute schistosomiasis is reported more frequently in S. japonicum where eggs production by worm pair is heavier than in S. hematobium & mansoni.

3- **Stage of repair by fibrosis**
   - Granulomatous tissue produced around the ova is replaced by fibrosis. The various clinical manifestations and complications will result according to the affected organ

Clinical features corresponding to the pathological stages

1- **Stage of invasion:**

- Cercarial dermatitis (swimmer's itch):
  - Severe itching due to cercarial penetration of the skin
  - More often due to other Schistosomes not pathogenic in humans
- Cercarial pneumonitis (eosinophilic pneumonitis): (4-6 wks)
  - It occurs with heavy infection.
  - There is patchy congestion of lungs.
  - Associated with eosinophilic sputum & high eosinophilia

2- **Stage of ova deposition & granuloma formation:** Acute schistosomiasis "Katayama syndrome":

- Ova deposition: Katayama syndrome
  - It's an initial febrile illness.
  - It's common with S. japonicum followed by S. mansoni & rare with S. hematobium.
  - It's mainly a problem in immigrants or visitors encountering cercaria for the first time. It's seldom seen in residents of endemic areas, perhaps because immune tolerance develops in utero due to transplacental passage of antigen
- Features of "Katayama syndrome:
  - Fever, urticaria and eosinophilia
  - Cough & wheezes
  - Diarrhea
  - Hepatosplenomegaly
  - Cachexia

3- **Granuloma formation:**

- In case of S. hematobium:
  - Terminal hematuria
  - Dysuria, frequency & precipitancy
  - Loin pains

- Hemospermia with detection of ova in semen if seminal vesicles, vas deferens of prostate is affected

- In case of S. japonicum & mansoni:.
  - Dysentery & tenesmus
  - Prolapse of anal mucosa
  - Anal fistula & fissures

4- Stage of fibrosis: Urinary bilharziasis:

- Urethral stricture.
- Urinary bladder lesions:
  - Wall thickening & contraction of the wall.
  - Cystitis & stone formation.
  - Cancer bladder; in Egypt the highest prevalence of cancer bladder is due to the prevalence of schistosomiasis.
- Ureteric lesions:
  - Stricture → hydroureter & hydronephrosis and renal failure.
  - Calculi due to stagnation of urine with superadded infection.
  - Secondary infection → pyoureter & pyonephrosis.
- Nodularity & thickening of spermatic cord and epididymis.
- In female genital tracts: vulva, vagina, uterus & Fallopian tubes and even ovaries may be affected. However, schistosomiasis is not a cause of infertility

5- Stage of fibrosis: Intestinal bilharziasis:

- Colonic polyposis:
  - Multiple sessile or pedunculated polypi in descending colon & rectum.
  - Polyp consists of a core of connective tissue containing the ova and covered by normal mucosa (they aren't adenomata i.e. they never turn malignant).
  - Polyposis may be extensive leading to protein-losing enteropathy.

- Bilharzioma:
    - Is a rare finding caused by massive deposition of ova with extensive reaction around → forming a large mass in descending colon that may be mistaken for malignant mass.
- Hepatosplenic bilharziasis:
    - Sometimes intestinal bilharzial ova may be washed up & get embolized through the portal tributaries → eventually leads to portal fibrosis with development of portal hypertension

Investigations

1- Direct methods:

- Urine analysis for S. hematobium:
    - Specimens collected between 10 am & 2 pm are most likely to contain eggs.
    - Urine sedimentation: eggs are sedimented by natural gravity.
    - Urine filtration: 24-h urine is passed through filter paper by vacuum or pressure.
    - Urine is examined by smear method after sedimentation or filtration for more than one time to be considered negative
- Stool analysis for S. mansoni & japonicum:
    - Direct smear examination isn't sufficiently sensitive.
    - Concentration techniques of feces are used such as formol-ether; thiomersal, iodine and formol (TIF) glycerol sedimentation (the simplest) or modified Kato smear
- Biopsy techniques for all schistosomal infections:
    - Rectal mucosa biopsy is obtained from a suspected lesion or rectal valves which are usually heavily infiltrated by bilharzial ova and examined by transparency technique (the sample is compressed between 2 slides & examined directly without stain under the microscope).

- Liver biopsy: examined by transparency technique or by histopathology

2- **Indirect methods:**

- Serology:
  - Detecting circulating antibodies by ELISA or IFAT
  - Disadvantages of serology:

    © It's not species specific

    © It doesn't reliably become +ve until 3 months after infection

    © Gives no indication of the intensity of infection

    © Doesn't distinguish between past & present infection

    © Requires high technology & often not commercially available for widespread use

3- **X-ray of urinary tract** to detect calcification of bladder & ureter

4- **Abd. U/S** to detect periportal fibrosis of the liver

Hepatic schistosomiasis

Etiology

1- **Repeated embolization** of S. mansoni ova (10-20% S. hematobium ova) into liver from colo-rectal venous plexus to be trapped in the portal vein tributaries → periportal fibrosis

2- **According to the size** of affected portal tract, there will be either "pipe stem" or fine periportal fibrosis

3- **Factors affecting morbidity of Schistosomiasis:**

- Worm load.
- Duration of infection.
- Nutritional status of the patient.
- Prevalence of hepatotoxins in the community e.g. pesticides.
- Concomitant hepatic viral infection.
- Immunologic background & genetic predisposition

Pathogenesis

1- **It is an immunologic disease:**
   - It's a delayed hypersensitivity reaction of cell mediated type produced by T-lymphocytes

2- **It is a mesenchymal rather than parenchymal disease:**
   - The portal tracts are thickened & many tributaries of the portal vein are obstructed leading to portal hypertension. The ultrastructure of hepatocytes is minimally affected i.e. hepatocytes aren't necrosed as in other types of hepatitis.

3- **Microscopically, there is:**
   - Periportal fibrosis with occasional bilharzial pigments in the phagocytes.
   - Complete obstruction of portal veins with formation of new network of vascular sheaths (angiomatoids).
   - Increased size & number of intrahepatic arterial branches which explains the maintenance of normal hepatic blood flow in the face of marked diminution of portal blood flow.

4- **The main pathology is due to** formation of granuloma that is replaced later by fibrous tissue → fibrosis which is responsible for all sequelae of the disease e.g. periportal fibrosis in liver, cor-pulmonale due to end arthritis oblitrans of the pulmonary arterioles

Clinical presentation

1- **Stage of hepatomegaly:**
   - The liver is enlarge, tender due to congestion as a result of deposition of embolized ova in portal tracts of liver

2- **Stage of hepatosplenomegaly:**
   - In addition to the enlarged liver, the spleen is also enlarged but not tender partly due to cellular hyperplasia & partly due to rise in portal pressure

3- **Stage of huge splenomegaly:**

- The liver is shrunken due to marked fibrosis, it is firm, its surface is finely nodular and it's not tender.
- The spleen is hugely enlarged due to portal hypertension, it is firm and its notch could be palpated.
- Portal thrombosis (due to slow portal blood flow) or hypersplenism may develop

4- Stage of ascites:

- In addition to huge splenomegaly, ascites appear lastly due to both hypoalbuminemia (due to hepatic dysfunction) & portal hypertension which localizes the oozed fluid in the peritoneal cavity.
- Causes of ascites in bilharzial liver fibrosis:
    - Hypoalbuminemia due to diminished synthesis of albumin by liver.
    - Portal hypertension that localizes the oozed fluid in the peritoneal cavity.
    - Oozing of lymph from the capsule of the liver.
    - Hyperaldosteronism due to inability of the liver to inactivate aldosterone → salt & water retention
    - Increased level of Antidiuretic hormone due to inability of the liver to inactivate it → water retention

5- Stage of hepatic cell failure & hepatic coma:

- It is a terminal stage due to:
    - Compression of hepatocytes by fibrosis & ascites.
    - Marked reduction of portal blood flow due to marked portal hypertension → ischemic affection of hepatocytes.
- The coma may be precipitated by:
    - Attack of hematemesis or melena.
    - Massive taping of ascites.
    - Massive diuresis.
    - Recurrent infection or diarrhea.

- Heavy protein meals.

Complications

1- **Huge splenomegaly:** that leads to
   - Hypersplenism → pancytopenia.
   - Splenic pain thrombosis; sudden abdominal pain & sudden enlargement of spleen. Doppler U/S is diagnostic.
   - Easy rupture of the spleen.
   - Divarication of recti & abdominal hernias

2- **Esophageal varices:** that may rupture → fatal hematemesis

3- **Ascites:** that is prone super infection → peritonitis
   - TB peritonitis: about 30% of patients with schistosomal ascites have some evidence of tuberculous peritonitis that might be due to:
     - Defective cell-mediated immunity
     - The ascitic fluid is suitable media for TB growth
   - Spontaneous bacterial peritonitis (SBP):
     - The route of infection is either:
       © Transmurally the intestinal wall
       © Through abdominal wall lymphatics
       © Through Fallopian tube in females
       © Iatrogenic following medical procedure e.g. paracentesis
     - The common invading organisms are either:
       © Enteric bacteria e.g. E. coli
       © Non-enteric bacteria e.g. pneumococci

4- **Schistosomal glomerulopthy (nephrotic syndrome):**
   - Due to autoimmune reaction resulting in deposition of antigen-antibody complex in glomerular vessels & Bowman's capsule.

5- **Chronic salmonellosis:**
   - Salmonella proliferate in the gut of adult Schistosomes being continuously shed into the blood leading to chronic bacteremia.
   - It presents with prolonged pyrexia & hepatosplenomegaly.

- Widal test is rarely positive. Diagnosis is made by blood cultures

6- Mixed shcistosomal hepatosplenic disease:

- Such mixed hepatosplenic disease has the worst prognosis.
- A large number of cases of schistosomal hepatosplenomegaly are mixed i.e. another etiology superadded mainly viral hepatitis (B&C). This leads to:
    - Higher carrier rates of the virus (HBV carrier rate is higher in bilharzial patients being 10-20% compared to 5% in general population).
    - Higher incidence of hepatocellular carcinoma (HCC incidence is higher in HBV infection combined with schistosoma compared to HBV infection alone).
    - Chronic persistent hepatitis.
    - Chronic active hepatitis.
    - Hepatic cirrhosis

Cardiopulmonary bilharziasis

Etiology [both S. ova & worms reach the lungs via]

1- Directly to the pulmonary arterioles causing acute necrotizing arteriolitis → leading to intimal thickening & even occlusion. With widespread deposition of ova in pulmonary arterioles there is reduction in the patent arteriolar bed & increased pulmonary vascular resistance → pulmonary hypertension → right ventricular hypertrophy (bilharzial cor-pulmonale).

2- Porto-systemic collaterals: ova from mesenteric veins are shunted to systemic veins then to pulmonary vessels

Pathology

1- Lung affection: by

- Cercaria during the invasion stage causing transient bronchitis or larval pneumonitis.

- Embolized ova with granuloma formation.
- Embolized worms which are harmless if living but when they die after treatment, they produce acute focal pneumonia (verminous pneumonia).

2- Heart affection by:

- Bilharzial pulmonary hypertension causes right ventricular hypertrophy with or without right ventricular failure.
- Embolized ova with granuloma formation causing miliary foci of fibrosis

Clinical features

1- Broncho-pulmonary:

- Larval pneumonitis: diagnosed by
  - Previous history for exposure to bilharziasis.
  - Plain X-ray; basal mottling.
  - CBC; leucocytosis with eosinophilia.
  - Good response to specific Antibilharzial treatment
- Verminous pneumonia:
  - Due to dislodgement of the worm in the ling either spontaneous or after treatment.
  - Treated by Antibilharzial drugs + ttt of pneumonia
- Asthmatic bronchitis:
  - Resistant to conventional anti-asthmatic drugs.
  - Ova, eosinophils & blood may be detected in sputum.
- Emphysema

2- Cardiovascular:

- Early; usually asymptomatic
- Late; right sided heart failure
  - Dyspnea & easy fatigue.
  - Chest X-ray: cardiomegaly.
  - ECG: high-peaked P-pulmonale, evidence of right ventricular hypertrophy & occasionally right bundle branch block

Chemotherapy of schistosomiasis

1- **Praziquantel:**

- Mode of action:
  - Increased influx of Ca & Na and decreased influx of K → muscular contraction of the parasite i.e. the parasite gets paralyzed.
  - Decreased glucose uptake → glycogen breakdown by the parasite.
  - Inhibition of egg formation by the female parasite
- Dose:
  - 40 mg/kg single oral dose is sufficient for all species. OR
  - 30 mg/kg for 2-3 doses may be necessary for S. mansoni & japonicum
- Indications:
  - It's effective against all human Schistosomes.
  - It has an effect on Fasciola & Cestodes
- Contraindications:
  - Pregnancy &lactation.
  - Lactation should be stopped for 72 hrs after receiving the drug
- Side effects:
  - Usually mild, there may be epigastric pain, nausea, dizziness, loose stool, pruritus and fever

2- **Metriphonate:** active against S. hematobium only

3- **Oxamniquine:** active against S. mansoni only

4- **Atremisinin:**

- Recently there is interest in the use of artemisinin derivatives in both treatment & prophylaxis particularly in China.
- This group of drugs is effective against the schistosomules as well as the adult worm. (see malaria)

5- **Niridazole**: it is imidazolidinone derivative

- Mode of action:
    - It affects vitelline glands of the worm → complete arrest of shell formation of the ova → eventually no eggs are seen in the uterus.
    - Affects male spermatogenesis, followed by complete destruction of the testes.
    - Decreased glucose uptake → glycogen breakdown by the parasite
- Dose:
    - 10-15 mg/kg per day for 20 days.
    - The dose can be divided twice daily
- Indication:
    - Effective against S. mansoni & hematobium.
    - Preferred in bilharzial polyposis as it can inhibit granuloma formation because it suppresses delayed hypersensitivity.
    - Treatment of Dracanculus medinensis
- Contraindications:
    - Patients with G6PD deficiency as it may cause hemolysis
- Side effects:
    - Most important; hyperexcitability, agitation, confusion, depression, hallucination & even generalized convulsions especially in patients with hepatosplenomegaly.
    - Less important; nausea, abdominal pain, diarrhea, skin rash & dark coloration of urine.

Ectopic schistosomiasis

Definition

1- Any pathological lesions produced by schistosoma ova or adults **outside the porto-caval venous circulation** including extension into the pulmonary arterioles.

Ectopic sites

1- CNS:

- Brain (cerebrum, cerebellum).
- Spinal cord
- Schistosomal granuloma in the nervous tissue takes a time to resolve & there is a concern that immunopathology gets worsen on treatment with praziquantel. Therefore adjuvant corticosteroids therapy is recommended

2- Genital system:

- Male: epididymis, hydrocele.
- Female: bilharzial ova have been detected in uterus & adenexa but rarely cause abortion or infertility

3- Skin: cutaneous bilharziasis; it occurs either

- Early: in the form of dermatitis during the invasive stage characterized by erythema or itchy papules.
- Late: non-specific allergic manifestation produced by products of Schistosomes e.g. fever, allergic erythema with joint pains.
- Perigenital granulomata: appears late in the disease in the form of granulomata around the urinary tract genitals due to ova deposition.
- Extragenital infiltrative lesions: rough papules or nodules in distant foci in the trunk due to ova deposition

4- Eyes e.g. conjunctiva & eyelids

Treatment

1- Early antibilharzial treatment even in suspected cases

2- Operative resection in there residual granuloma followed by Antibilharzial treatment.

Diphyllobothrium latum

Pathogenesis

1- Infective stage → plerocercoid larva in fish muscles

2- Definitive host → man – dogs and cats – fish eating animals

3- Habitat → small intestine

4- I.H.

- 1st → Cyclops (procercoid larva)
- 2nd → fresh water fishes (سلمون والسردين) – plerocercoid larva = sparganum

5- **Mode of infection**

- Ingestion of plerocercoid larva in raw or improperly cooked or unsalted fresh water fishes (adult in 6 weeks)

Clinical features

1- **Digestive disturbances** (intestinal irritation)

- Nausea, vomiting, diarrhea, colic and anorexia

2- Wight loss and hunger pains

3- **Neurological manifestations**

- In the form of headache, insomnia or convulsions caused by the absorbed worm by-products

4- **Pernicious anemia** (Macrocytic hyperchromic):

- As the parasite competes with the host for the available supply of vitamin B12 leading to its deficiency
- Also caused by some toxins secreted by the parasite

5- **Mechanical obstruction** by large number of worms

Diagnosis

1- **Stool examination**

- Show operculated eggs or
- Worm segments

2- **CBC** → pernicious anemia

Treatment

1- **Praziquantel**

- The drug of choice
- Single oral dose of 10 mg/kg body weight

2- **Niclosamide (Yomesan)**

- Single oral dose of 2 gm (4 tab.) for adults and 1 gm for children
- These chewable tablets should be taken after light breakfast
- يحطم الديدان

3- **Quinacrine HCL (Atebrine)**

- 0.8 gm in divided doses (0.2 gm every 10 min.) on empty stomach followed 2 hours by saline purge as the drug causes temporary detachment of the scolex from the intestinal mucosa

4- **Supportive treatment**

- Parenteral vitamin B12 for anemia

Diphyllobothrium mansoni

Pathogenesis

1- Infective stage

- Procercoid larva in Cyclops
- Plerocercoid larva in tissues of 2nd I.H (sparganum)

2- Definitive host → dog and cat

3- Habitat → small intestine

4- I.H.

- 1st → Cyclops
- 2nd → frogs, snakes, birds, pigs and man

Sparganosis

Definition

1- Presence of sparganum mansoni or sparganum proliferum in human tissues (man act as I.H. in a blind cycle)

Types of spargana

1- Sparganum mansoni → Plerocercoid larva of D. mansoni

2- Sparganum proliferum → plerocercoid larva of D. proliferum

Mode of infection

1- **Drinking** water with infected Cyclops (the procercoid larva migrates to human tissue and develop into plerocercoid larva)

2- **Eating** improperly cooked tissues of 2nd I.H containing plerocercoid larvae

3- **Local application of tissues** of 2nd I.H as poultices لبخة to inflammed tissue e.g. eye or skin → plerocercoid migrates to human tissue where the poultice is applied

Clinical features

1- **Symptoms depend on the tissue invaded**

- Degenerated larvae cause inflammation and necrosis but no fibrosis

2- **Common sites are:** SC tissues, eye, LN, peritoneal cavity or any other site

3- **SC tissue**

- Inflammatory tender swellings

4- **Eye**

- Painful edematous conjunctivitis
- Ptosis
- Irritation and lacrimation
- Subconjunctival nodules

5- **Patient may suffer from**

- Urticaria, edema, fever, pain and eosinophilia

Diagnosis

1- Cannot be settled except **after surgical removal** and identification of plerocercoid larva in the removed tissue

Treatment → surgical removal (difficult in sparganum proliferum)

Taenia saginata

Pathogenesis

1- Infective stage → cysticercus bovis in beef

2- Definitive host → man

3- Habitat → small intestine

4- I.H. → cattle

5- Mode of infection

- Ingestion of cysticercus bovis in raw or improperly cooked beef (steaks, hamburgers, kabab) –adult in 3 months-

Clinical features

1- Digestive disturbances (intestinal irritation)

- Nausea, vomiting, diarrhea, colic and anorexia

2- Wight loss: as the parasite consumes much of the food of the patient

3- Neurological manifestations

- In the form of headache, insomnia or convulsions caused by the absorbed worm by-products

4- Mechanical obstruction: by a rolled mass of worms

5- Appendicitis or cholangitis : caused by stray segments of the worms

6- Perianal irritation and itching and worry of the patient: due to migration of the segments out of the anus

7- May appear in the vomit of any reason

Diagnosis

1- **Clinical**

- In most infections, the patient notices the white motile segments in the faeces, under clothes or in bed

2- **Detection of eggs**

- Faecal smear or
- Anal swabs

3- **Searching for gravid segments in faeces**

- If not found, give a saline purge. Compress the segments between 2 slides and count the main lateral branches
- Eggs of T.saginata are similar to eggs of T.solium, so differentiation made by gravid segments [eggs of T.saginata is stained well by Z.N. stain while eggs of T.solium is not]
- In T.saginata → gravid segments usually detach singly, pass out mixed with faeces or creep out of the anus without defecation and the lateral branches on each side count 15-30 (18). While in T.solium, gravid segments detach in groups about 5-6 and come out mixed with faeces during defecation with lateral branches count 7-12 (9)

Treatment [as D.latum]

1- Praziquantel
2- Niclosamide
3- Quinacrine HCL

Taenia solium

Pathogenesis

1- Infective stage → cysticercus cellulosae in pork

2- Definitive host → man

3- Habitat → small intestine

4- I.H. → pig (muscles of the tongue, shoulder, neck and diaphragm)

5- Mode of infection

- Ingestion of cysticercus cellulosae in undercooked pork (→ adult)

Clinical features

1- Similar to T.saginata (but no perianal itching) +

2- Cysticercosis ®

- When man ingests eggs of T.solium → the larval stage (cysticercus cellulosae) develops in the extraintestinal tissues leading to a condition known as cysticercosis
- This condition is likely to occur with T.solium not with T.saginata a fact which makes T.solium a more serious parasite

Diagnosis → similar to T.saginata

Treatment [doses similar to D.latum but]

1- Praziquantel and niclosamide

- Should be avoided, as they disintegrate the worms → releasing large numbers of eggs in the lumen of the intestine → increased possibility of cysticercosis due to internal autoinfection
- If given, a saline purge must be given 1-2 hours later to accelerate removal of eggs

2- Quinacrine HCL (Atebrine)

- It is preferable because it leads to expulsion of the intact worms
- The scolex should be obtained intact otherwise division of the neck segment can regenerate the whole worm again
- The drug cause nausea and vomiting and so an antiemetic must be given 1 hour before to avoid reversed peristalsis and internal autoinfection

Cysticercosis

Definition

1- Invasion of human tissues by **cysticercus cellulosae the larval** stage of T.solium [man acts as I.H. in a blind cycle]

Infective stage → eggs

Mode of infection

1- Heteroinfection

- Ingestion of food (green raw vegetables) or drink contaminated with eggs

2- External autoinfection

- Hand to mouth infection in a patient having adult worms in his intestine

3- Internal autoinfection

- In a patient having adult worms in his intestine, reversed peristalsis may carry some detached segments to the stomach and upper small intestine to be dissolved there by the action of juice enzymes thus liberating the ova or dissolution of gravid segments by some drugs as niclosamide

Pathogenesis

1- **The severity** of the condition depends on the size, number and the site of the larvae

2- **The eggs** → onchosphere larva → penetrates the mm → blood → different tissues especially SC tissue, eye, brain,muscles, heart and elsewhere

3- It develop into cysticercus cellulosae → **cyst formation** → chronic inflammation, fibrosis and calcification

Clinical features

1- Initial phase → pain and swelling accompanied by esinophilia

2- **SC tissues** → easily palpated movable small painless nodules esp. on the arms or chest (resemble small lipomas)

3- **Eye** → visual disturbances

4- **Brain**
    - Neurocysticercosis leading to variable neurological disorders as epilepsy, increased ICT and hydrocephalus
    - About 15-25% have a tapeworm at presentation or have a past history of tapeworm infection
5- **Muscle cysts** → eventually calcify, usually on the forearms, psoas or thigh muscles
6- Patient may suffer from
    - Muscle pain, fever and eosinophilia

Diagnosis

1- **History** of infection with adult T.solium is suggestive
2- **Eosinophilia**, intradermal tests and serological methods as IHA and ELISA
3- **Biopsy** → from a nodule in the skin or muscles
4- X-ray → to visualize calcified lesions e.g opaque calcified cysts in the body muscles as pectoral region (spindle shaped shadows < 2cm)
5- CT, MRI, U/S and ophthalmological examination → help to localize the lesions
6- CSF → may contain eosinophils and increased protein mostly IgG

Treatment

1- **Albendazole**
    - 15 mg/kg/day (max. 800 mg/day) for 10-28 days
    - Recommended especially for active brain cysts (neurocysticercosis)
2- **Praziquantel**
    - 50-100 mg/kg/day in 3 divided doses for 14 days
    - Used as a 2nd choice in active parenchymal neurocysticercosis
3- **Cimetidine** → 400 mg 3 times daily may be used to increase the levels of both albendazole and praziquantel
4- **Corticosteroids**
    - Simultaneous use of steroids is essential to relieve the intense local inflammatory reactions of the antigenic material released from dead larvae (inflammation around damaged cysts)

- Steroids also needed in neurosurgical doses for short term management of occasional flare-ups of inflammation and cerebral edema that occur as cysts degenerate as part of their natural history
- Dexamethasone 6-12 mg/day in divided doses should be given before and during antiparasitic treatment
- Dexamethasone ↑ levels of albendazole and ↓ levels of praziquantel

5- Inactive parenchymal cysts

- Do not require treatment with antiparasitic agents

6- Symptomatic e.g. epilepsy

7- Vitamin D and calcium to help calcification

8- Surgery

- Shunting may be required for obstructive hydrocephalus and intracranial hypertension
- Extraparenchymal cysts may require treatment with combinations of antiparasitic drugs, steroids and possibly surgery

Hymenolepis nana

Pathogenesis

1- Infective stage

- Egg
- Cesticercoid larva in body cavity of vectors (flea larva or grain beetles)

2- Definitive host → man esp. children & rat, mice

3- Habitat → small intestine

4- I.H. → man, various insects (fleas, beetles)

5- Mode of infection

- Direct ingestion of eggs along contaminated food, water and hands
- Internal and external autoinfection
- Ingestion of cysticercoids in infected insects along contaminated food and drink

6- **The parasite spreads easily** and tends to occur in groups of people living together
    - As no external development required
    - And no special I.H. needed

Clinical features

1- Asymptomatic → in light infection
2- Tends to occur more in **children**
3- **Intestinal disturbances (irritation)**
    - Vomiting, recurrent diarrhea, abdominal pain, anorexia
4- **Nervous manifestations**
    - Dizziness, insomnia and convulsions due to absorption of metabolic by-products

Diagnosis

1- Detection of **eggs** in faecal smear

Treatment

1- **Praziquantel**
    - The drug of choice
    - **25** mg /kg single oral dose is highly effective
    - Treatment should be repeated after 10 days due to liberation of cysticercoids from submucosa into the intestinal lumen
    - Affect adults and larvae
2- **Niclosamide**
    - 2 gm/day for 5-7 days
    - Affect adult worms only
    - Treatment should be repeated after 3 weeks to remove newly developed worms from hidden cysticercoids
3- **Treat all members** of the family at the same time

Hymenolepis diminuta

Pathogenesis

1- Infective stage → cysticercoids larva in body cavity of vectors

2- Definitive host → rat, mice and rarely man

3- Habitat → small intestine

4- I.H. → various insects (fleas, beetles, cockroaches)

5- **Mode of infection**

- Ingestion of cysticercoids larva in infected insects along contaminated food and water

Clinical features

1- Usually asymptomatic

2- Occasionally, mild GIT disturbances occur

Diagnosis & treatment → as H.nana

Dipylidium caninum

Pathogenesis

1- Infective stage → cysticercoid larva in body cavity of vectors

2- Definitive host → dog, cat and occasionally man especially children

3- Habitat → small intestine

4- I.H. → various insects e.g. dog, cat and human fleas larvae

5- **Mode of infection**

- Ingestion of cysticercoid larva in infected fleas

Clinical features

1- Often asymptomatic

2- **Abdominal pain and diarrhea** may occur

3- Urticaria and eosinophilia

Diagnosis

1- Detection of **gravid segments or egg capsules** in the stools

2- Rarely eggs can be detected

Treatment → as T.saginata

Multiceps multiceps (Coenurosis)

Pathogenesis

1- Infective stage → eggs

2- Definitive host → dog and other canines

3- Habitat → small intestine

4- I.H. → herpivorous animals as sheep, goats and cattle & occasionally man

5- Mode of infection

- Ingestion of eggs along contaminated food or water
- Handling dogs whose hairs are contaminated with eggs

6- Coenurosis

- Human infection with coenurus cerebralis; the larval stage of multiceps multiceps
- The coenurus cyst develops chiefly in the brain and spinal cord
- Characters of the cyst
    - Hen's egg in size, full of non antigenic fluid, translucent and lined with germinal layer only
    - Contains few macroscopic scolices (no broad capsules or daughter cysts)

Clinical features

1- In animals → disturbed gait (Gid disease)

2- In man

- Symptoms of increased ICT
- Nervous symptoms depend on its location

Diagnosis

1- Usually diagnosed as brain tumor and identified **after removal**

Treatment → surgical removal

Management of intestinal cestode infections

1- Praziquantel

- Single oral dose 10 mg/kg is the drug of choice
- H.nana requires 25 mg/kg as a single dose
- Caution is advised in populations in which cysticercosis is common → because of the risk of precipitating or aggravating neurological symptoms

2- Niclosamide

- Single oral dose (500 mg if < 11 kg; 1g if 11-34kg; 1.5 g if > 34 kg; 2 g for adults) is also effective
- Tablets should be well chewed and swallowed with plenty of water
- The routine use of purgatives and antiemetics in patients with T solium prior to cestocidal treatment in order to prevent retrograde peristalsis of eggs and possible risk of cysticercosis is not justified on the basis of clinical evidence

3- Albendazole

- Used in treatment of cysticercosis and hydatid cyst
- Effective also in treating intestinal taeniasis

4- Nitazoxanide

- Effective in infections with T. saginata and H. nana

Hydatid disease

1- **Hydatid cyst disease** → Echinococcus granulosus

2- **Alveolar hydatid disease** → Echinococcus multilocularis

Hydatid cyst disease

Pathogenesis

1- Infective stage → egg

2- Definitive host → dogs and other canines

3- Habitat → small intestine

4- I.H. → herbivorous animals (sheep, cattle, camels) and occasionally man

5- **Mode of infection**

- Ingestion of eggs along food or water contaminated with faeces of dogs
- Handling dogs whose hair are usually contaminated with eggs (eggs → hydatid cyst) –hand to mouth infection-

6- **Hydatid cyst ***

- The fully developed cyst is typically unilocular, spherical in shape and filled with fluid
- It reaches a diameter of 10 cm or more (this takes many years)
- The cyst wall is differentiated into the following layers from inside to outside:
  - Cellular or germinal layer capable of division
  - Elastic non cellular laminated layer
  - Host produced fibrous tissue layer to prevent further growth of the cyst
- The cyst contains
  - Individual scolices (microscopic, about 100-1000)
  - Daughter cysts similar to mother cyst
  - Brood capsules which are sacs enclosing a number of scolices

- Scolices, daughter cysts and broad capsules may remain attached to the wall of the mother cyst or may be detached and fall in the cavity (called hydatid sand)

- Exogenous daughter cyst occurs as a result of herniation of germinal layer to the outside
- Sometimes, the germinal layer of the mother and daughter cysts and brood capsules fail to give scolices thus we get a sterile cyst

Clinical features

1- <u>Hepatic cyst</u> (66-70%) usually in the right lobe→ see hapatology

2- <u>Pulmonary cyst</u> (20-22%):

- Mostly asymptomatic and found incidentally on chest X-ray
- Early symptoms include:
  - Fever
  - Cough and Haemoptysis
  - Transient thoracic pain
  - Dyspnea
- In majority of cases, the cyst transfers into chronic pulmonary abscess (if rupture is incomplete) and the patient complains of
  - Sudden attack of cough
  - With sputum containing frothy blood, mucus and hydatid material
- Rupture into the lung may cause
  - Pneumothorax
  - Empyema
  - Hypersensitivity
- Seeding is uncommon
- Rupture into a bronchus may cause the patient to cough up clear salty tasting liquid, sometimes followed by the soft white outer membrane of the cyst

3- <u>Brain cyst</u> (1%):

- Large cyst leads to symptoms of ↑ICT up to epilepsy

4- <u>Renal cyst</u> (3%):

- It leads to intermittent pain and hematuria
- The hydatid sand may be present in urine

5- Osseous cyst (2%):

- It has no fibrous tissue layer nor laminated layer, but only germinal layer which develops first in the marrow cavity then extends to the osseous tissues leading to
    - Erosion of large area of bones
    - Destruction of the trabeculae
    - Bony pains and spontaneous fracture

6- Eye

- Proptosis
- Chemosis

7- May also occur at **other sites** as spleen

8- General effects due to rupture or leakage of cyst fluid (due to ↑ tension, trauma surgery or 2ry infection)

- Hypersensitivity reactions ranging from urticaria, pruritus and fever to fatal anaphylaxis (due to release of highly antigenic hydatid fluid)
- 2ry cysts (due to implantation of germinal cells in other tissues as peritoneal cavity)
- Leakage into the biliary tree may cause colic, urticaria and obstructive jaundice, sometimes complicated by 2ry bacterial infection

Diagnosis

1- Clinical

- History of close contact with dogs
- Slowly growing cystic mass + hydatid thrill

2- Direct methods;

- X-ray esp. in pulmonary cysts and calcified cysts
    - Round solitary or multiple sharply contoured cysts of 1-15 cm in diameter
    - Internal daughter cysts give a car wheel appearance

- Thin crescent or ring shape calcifications
- Collapsed pulmonary cyst may have a characteristic water lily appearance

- U/S:
  - Detect uncalcified cysts and of value in the follow up of treated cases
  - Useful for abdominal cysts
- CT, MRI, X-ray
  - Useful for detecting cysts elsewhere
- Aspiration cytology
  - Using trichrome staining of the filtered aspirate to show acid fast hooklets (component of hydatid sand)
  - This procedure is risky and may cause transplantation of the germinal layer and formation of new cysts or anaphylactic shock
- Finding hydatid material
  - After surgical removal of the cyst or
  - Finding hydatid fragments from a ruptured cyst in the sputum or urine

3- Indirect methods:

- Eosinophilia may follow leakage or rupture
- Serological tests
  - The specific IgG ELISA antigen B-rich fraction (AgB) → is the most sensitive serological test
  - Enzyme linked immunotransfer blot assay (EITB)
  - Double diffusion test for arc 5 (DD5): may give false +ve results in patients with cysticercosis
  - Current serological tests lack sensitivity for extrahepatic cysts
- Molecular diagnosis by DNA analysis and PCR
- Urine antigen detection tests are promising
- Intradermal test of Casoni

- 0.2 cc of sterile hydatid fluid is injected intradermally in one arm (test) and similar amount of saline in the other arm as control
- In +ve cases → local wheal within 20 min surrounded by an erythematous zone
- False +ve results occur in 18% of cases
- Negative results occur if the test done before 1 month of the onset of disease
- Now, it is not preferred because it may lead to allergic reactions

Treatment

1- Surgical removal

- Was the preferred method in the past for managing accessible cysts
- Small cysts can be removed intact
- Large cysts should be carefully aspirated and the aspirate replaced with an equivalent volume of a scolicide such as hypertonic saline, reaspirated after 5-10 min and the procedure repeated. Following reaspiration, the cyst cavity is opened, the membranes are removed and the cavity closed. Great care should be taken to avoid spillage of cyst fluid

2- PAIR

- Now used increasingly as an alternative to surgery
- Principle:
  - Puncture aspiration injection (of hypertonic saline or other scolicidal fluid e.g. hydrogen peroxide or ethanol) and reaspiration (after 20 min)
  - Cyst puncture is done under sonographic or CT guidance
- Indications:
  - Non echoic lesion > 5cm in diameter
  - Cysts with daughter cysts and/or with detachment of membranes
  - Multiple cysts if accessible to puncture
  - Infected cysts

- Preferred for hepatic and pulmonary cysts

- PAIR is also recommended for
  - Pregnant women
  - Patients who fail to respond to chemotherapy alone
  - Patients in whom surgery is contraindicated
  - Patients who refuse surgery
  - Patients who relapse after surgery
- Contraindications
  - Non cooperative patients, children < 3 yrs
  - Inaccessible or risky location of the cyst e.g. spine, brain, heart
  - Inactive or calcified lesion
  - Cysts communicating with the biliary tree
  - Cysts opening into the abdominal cavity, bronchi and urinary tract

3- Laparoscopic treatment of hepatic and splenic cysts is also effective

4- Medical treatment

- Indications
  - Patients with inoperable widespread or numerous cysts
  - Patients who are unfit for surgery
  - Patients undergoing surgery or PAIR should receive albendazole either alone or in combination with praziquantel for 1-3 months prior to, and covering the procedure
  - PAIR should be followed by an 8-week course of albendazole
  - Antihelmintic treatment may reduce the need for surgery in patients with uncomplicated pulmonary cysts
- Regimen
  - Albendazole 400 mg twice daily for adults (5-7.5 mg /kg twice daily for children) for 28 days
  - Followed by 14 days rest

- Then repeated for 3-12 cycles depending on response, although many experts now just give continuous therapy without the 14 days rest periods
- Albendazole absorption is enhanced if taken with fatty meals

- Albendazole plus praziquantel
  - Has been shown to have greater protoscolicidal activity in animal studies and in vitro compared with either drug alone
  - Combined therapy has been used successfully in managing inoperable spine, pelvic, abdominal, thoracic and hepatic hydatosis and as an adjunct to surgery

Alveolar hydatid disease

Pathogenesis

1- Infective stage → eggs

2- Definitive host → foxes, wolves and cats

3- Habitat → small intestine

4- I.H. → rodents and occasionally man

5- Mode of infection

- Ingestion of eggs from contaminated hands while handling foxes or wolves during trapping or skinning
- Ingestion of food or drink contaminated by faeces of the infected animals
- Ingestion of eggs from contaminated wild ground fruits such as bilberries and their close relatives, lingonberries and cloudberries, widely eaten in northern Europe (the main route in such areas)

6- The alveolar cyst

- It is a porous spongy gelatinous mass, usually sterile

- Formed of small irregular cavities that are lined by germinal layer with a very thin or no laminated layer with fibrous tissue strands in between the cavities

Clinical features

1- Unlike E.granulosus

- The cyst produces daughter cysts by external and not internal budding, so it tends to invade progressively into surrounding tissues like a malignant tumor and is not contained in a well defined fibrous capsule (not defined from the surrounding tissues)
- There is degeneration and calcification in the centre

2- It may be **30 yrs before** the patient becomes symptomatic

3- 1ry site of tissue invasion

- Usually the liver (90-100%), mimicking hepatic carcinoma or cirrhosis
- Usually there is right upper quadrant pain, hepatomegaly and a palpable mass

4- Metastatic lesions

- May occur in other tissues (lung, brain, bone)
- Evident in > 10% of patients

5- Complications

- Occur in about 2% of cases
- Due to local invasion or as a result of metastatic lesions involving brain, lung or mediastinum
- Untreated, 90% of patients die within 10 yrs of presentation

Investigations

1- U/S, CT, MRI and serology → useful in establishing the diagnosis

2- Histology → provides confirmation

Treatment

1- Surgery

- Excision is preferred for the primary lesion
- Pre and post operative treatment with albendazole is recommended

2- Medical treatment

- Indications
    - Inoperable patients
    - Postoperatively
- Regimen
    - Albendazole 10 mg/kg in cycles of 28 days followed by 14 days rest
    - Cycles usually continued for more than 1 year
    - Mebendazole 40-50 mg/kg/day also used extensively, sometimes for up to 10 years

3- Prognosis

- Serology may remain +ve several years following successful treatment
- A 90% 10 year survival rate is possible with early diagnosis and appropriate treatment

ENTOMOLOGY

Arthropod	Medical importance
Culex mosquitoes	1- W.bancrofti (main) 2- Viral encephalitis 3- Rift Valley fever
Aedes mosquitoes	1- Yellow fever virus 2-Dengue fever virus 3- W. bancrofti 4-Rift Valley fever
Anopheles mosquitoes	1-Human malaria 2-W. bancrofti & B. malayi 3-Viral encephalitis (occasionally)
Phlebotomus (Sand fly)	1-Protozoal → Leishmaniasis 2-Bacterial → Oroya fever (Bartonellosis) 3-Viral → Sand fly fever (3 day fever) 4-Harrara
Musca domestica (House fly)	1-Bacterial - Enteric fever - Bacillary dysentery - Cholera - Wound infection 2-Viral - Poliomyelitis - Hepatitis A - Trachoma 3- Parasitic - E. histolytica cyst - Giardia lamblia cyst -Eggs of ascaris, enterobius, trichuris, H.nana, T. solium 4- Accidental myiasis e.g. intestinal myiasis
Stomoxys calcitrans (Stable fly)	1-Polymorphic trypanosomes 2-Poliomyelitis 3-Anthrax bacilli 4-Painful bite 5-Accidental myiasis 6-Skin allergy
Glossina (Tsetse fly)	1-G. palpalis → Trypanosoma gambiense 2-G. morsitans → Trypanosoma rhodesiense 3-Nagana (fatal disease to animals)
Oestridae (Ostrus, Hypoderma, Dermatobia, Gastrophilus)	Specific myiasis

Calliphoridae (Calliphora, Lucilia, Sarcophaga, Wohlfahrtia)	Semi-specific myiasis
Simulium (Black fly)	I.H. for onchocerca volvulus
Chrysops	I.H for loa loa
Fleas	1-Plaque → Xenopsylla cheopis, Ceratiphyllus fasciatus 2-Endemic typhus (Murine) → rat fleas 3-Chigger's disease → Tunga penetrans (sand flea) 4-Rat fleas act as I.H. to H.nana and H.diminuta 5-Dog and cat fleas act as I.H. to D.caninum 6-Dermatitis and allergy
Lice	1-Pediculus humanus corporis - Epidemic typhus - Epidemic relapsing fever - Trench fever (5 days fever) 2-Vagabond's disease 3-Phthirus pubis - Blepharitis - Irritation and itching
Bugs	1-Triatoma (Winged bug) -Trypanosoma cruzi (Chaga's disease) 2- Cimex lectularius (Bed bug) - Local urticaria - Insomnia and nervous irritability - May transmit HBV
Hard ticks (Ixodidae)	1-Bacterial -Tularaemia 2- Rickettsial - Q fever - Rocky mountain spotted fever - Boutonneuse fever 3-Spirochaetal - Lyme disease 4- Viral - Hemorrhagic fever - Tick borne encephalitis - Colorado tick fever 5- Protozoal - Babesiosis 6-Tick paralysis (ascending flaccid) 7- Dermatosis and mechanical injury at site of the bite
Soft ticks (Argasidae)	1-Endemic relapsing fever 2-Q fever 3-Tick paralysis (ascending flaccid) 4-Dermatosis and mechanical injury at site of bite
Mites	1-Sarcoptes scabiei - Scabies 2- Demodex folliculorum

	- Acne and comedones - Blepharitis, dry erythema with scaling 3- Trombiculid mites - Scrub typhus (Trombicula akamushi) - Dermatitis (Chigger's mites) 4-House dust mites - Bronchial asthma esp. in children - Perinnial rhinitis - Dermatitis 5- Storage mites - Dermatitis - Allergic conjunctivitis - Intestinal acariasis - Respiratory acariasis 6- Domestic mites - Blood sucking causing dermatitis
Cyclops	I.H. for D. latum, D. mansoni and D. medinensis
Scorpion	- Scorpion sting is very painful - Its toxin causes twitching, muscle spasms, convulsions, shock and may cause heart failure esp. in children , elderly and debilitated persons

Medical importance of arthropods

1- Arthropods as disease agents
   - Dermatitis and allergic skin lesion by the bite e.g. lice, mosquitoes, bugs
   - Inoculation of poisons e.g. ticks, scorpions, spiders
   - Tissue invasion e.g. myiasis, scabies
   - Entomophobia

2- Arthropods as vectors of diseases
   - Mechanical transmission
     - Direct e.g. mouth parts of bitting stable fly (pick and inoculate)
     - Indirect (contamination on mouth parts, hairs, legs) e.g. house fly
   - Biological transmission
     - Propagative (multiply) e.g. Y.pestis in fleas, Yellow fever virus in Aedes
     - Cyclodevelopmental (cyclic change) e.g. microfilaria of W.bancrofti in culex
     - Cyclopropagative (multiply & cyclic change) e.g. malaria in anopheles, leishmania in sand fly
     - Transovarian (transmission to generations through eggs) e.g Trombicula akamushi in R. orientalis, organisms transmitted by hard ans soft ticks
     - Trans-stadial (stage to stage) e.g. organisms of scrub typhus which pass from larvae (as ectoparasite of man) to nymph to adults to next larvae.

Classifications of arthropods

Insecta	Diptera	- Mosquitoes - Phlebotomus (sand fly) - Simulium (black fly) - Culicoides - Chrysops - Muscidae - Calliphoridae - Oestridae
	Siphonaptera	- Fleas
	Anoplura	- Lice
	Hemiptera	- Bugs
Arachnida	Ticks	
	Mites	
	Scorpion	
Crustacea	Cyclops	

Scabies

Pathogenesis

1- Cause → the mite "sarcoptes scabiei"

2- Habitat → tunnels in the corneal layer of the skin

3- Mode of infection → direct skin contact or less frequent, through towels, clothing or bed linen

Clinical features

1- Incubation period → 4 – 6 weeks

2- More common in children

3- **Sites** → interdigital spaces, flexor aspects of the wrist, forearm, elbow, axillae, back, inguinal region or genitalia

4- **The classic diagnostic lesion** → is the interdigital burrow from which mite can be sometimes extracted with a sterile needle

5- **Always considered scabies in the following situation**

- Intense itchy generalized rash (elevated reddish tracks with minute vesicles) esp. in a child
- History of nocturnal itch which ↑ by warmth and sweating → scratching the skin يقطع الجلد
- Positive family history

6- **The classic lesions not always seen as**

- 2ry bacterial infection and/or allergic hypersensitivity to the mite can alter the rash significantly (infected papules, widespread vesicles and popular urticaria may occur)
- Excoriation of the rash alter its appearance

7- **Norwegian or crusted scabies**

- Occur in immunocompromised patients e.g. HIV or lepromatous leprosy or may occurs sporadically for no obvious reason (common in Australian aborigines)

- Represent massive proliferation of the infecting mites (hundreds of mites in the lesion)
- Clinically
    - Generalized dermatitis with extensive scaling and crusting
    - Frequently, not as itchy as classical scabies

Treatment

1- Topical treatment

- Applied from the neck down to all parts of the skin, with particular attention to crevices and the genitalia
- All household contacts must be treated at the same time
- For severe cases → the treatment should be repeated 5-7 days later
    - Permethrin 5% cream → the treatment of choice, if available
    - Benzyl benzoate 25% → best avoided in children < 4 yr
    - Sulphur 6% ointment → better alternative for children > 4 yr

2- Oral treatment

- Ivermectin 200 µg/kg as a single oral dose → effective esp. in difficult cases

3- Symptomatic treatment

- Calamine lotion and antihistaminics → for itching (itching may continue for some weeks after effective treatment)

4- Prevention

- General principles of hygiene
- Tetmosol (5% tetraethylthiuram mono-sulphide) soap or rubbing oils

Approach to syndromes/symptom complexs

Sexually transmitted diseases

Common causes of genital discharge

1- **Urethral discharge in males [vaginal discharge in females]**
   - Gonorrhea
   - Chlamydial infections

2- **Vaginal discharge in females**
   - Vulvovaginal candidiasis
   - Trichomoniasis
   - Bacterial vaginosis

Common causes of genital ulcers

1- Chancroid or soft sore

2- Syphilis

3- Lymphogranuloma venereum or inguinale

4- Donovanosis [granuloma venereum or inguinale]

5- Genital herpes

6- Genital warts

Causes of high incidence of STD in developing countries

1- Main population young adults

2- Prostitution

3- Rural urban migration

4- Lack of adequate medical services

5- Polygamy

6- Antibiotic resistant strains

Syndrome	Infectious causes	Aetiological agent	Non infectious causes
Genital discharge			
Urethral discharge	Gonococcal urethritis	N. gonorrhoeae	Physiological Trauma
	Non gonococcal urethritis	No etiology (25%) C. trachomatis (most of the rest) Ureaplasma urealyticum Trichomonas vaginalis Candida albicans	
	Intra-uretheral ulcers or warts	Herpes simplex HPV	
Vaginal discharge	Vaginal infections	C. albicans Gardnerella vaginalis T. vaginalis	Physiological Trauma Retained products Tampons
	Cervical infections	C. trachomatis N. gonorrhoeae Herpes simplex HPV Treponema pallidum	Carcinoma of cervix (linked with HPV infection)
Genital ulcer			
Multiple and painful	Herpetic Chancroid Scabies	Herpes simplex Haemophilus ducreyi Sarcoptes scabiei	Behcet's disease Stevens-Johnson syndrome
Single and painful	TB Superinfection of painless ulcers	M. tuberculosis Staph. Aureus	Carcinoma Trauma
Multiple and painless	2ry syphilis	T. pallidum	
Single and painless	1ry syphilis LGV Granuloma inguinale	T. pallidum C. trachomatis (LGV str) Calymmatobacterium granulomatis	
Bubo			
Genital ulcer visible	Chancroid	H. ducreyi	
No genital ulcer visibl	LGV	C. trachomatis	
Non sexually transmitted infections	Plaque Filariasis Infections of the lower limb		

Gonorrhea

Causative organism

1- **N. gonorrhea** → gram –ve oval dipplococci

2- **Single exposure** can cause the disease in 20% of males which is higher than females

Incubation period

1- About 2 – 5 days

2- About 90% will develop symptoms within 14 days

3- Asymptomatic infections are more common in females

Clinical features

1- **In males**

- Thick yellow urethral discharge
- Meatal itching
- Dysuria, frequency and edema

2- **In females**

- Vaginal discharge and dysuria

3- **Other features**

- Infection of pharynx and rectum can occur
- The rectum is easily infected in males from infected vaginal discharge
- Vulvovaginitis in sexually abused children can occur

Complications

1- **In males**

- Unilateral epididymitis which also occur in
  - Chlamydia
  - Mumps
  - Gram –ve bacilli
- Sterility

2- In females

- Infection of bartholin's gland
- Spread of infection to uterus and fallopian tubes
- Sterility

3- Disseminated infection

- Occur in 2% of cases
- Leading to oligoarthritis and tenosynovitis

4- Ocular gonococcal infection

- Due to autoinoculation with contaminated fingers
- In the form of acute purulent conjunctivitis

5- Ophthalmia neonatorum

- Occur in 1st month of life in pregnant females in tropical countries
- It is acute bilateral purulent conjunctivitis which may lead to blindness
- Diagnosis → microscopy gram stain for gono. and Gemsia stain for Chlamydia & culture
- Treatment → 1% silver nitrate installation or 1% tetracycline ointment of eyes at delivery

Diagnosis

1- In males

- Gram –ve diplococcic of urethral smears by insertion and rotation of swab in the urethra for 5 min

2- In females

- Ectocervix is wiped clean and swab is taken from cervical os & rotated for 10 min

3- Also, rectal swab can be done or from joints or blood culture

4- Antigen detections

- Immunoflurescence
- ELISA
- Detection of gonoc. DNA

Treatment

1- **Ceftriaxone or ciprofloxacin**
   - To guard against penicillinase producing N. gonorrhea
   - Treatment for 7 days in disseminated infection

2- **Penicillin, tetracycline and co-trimoxazole**
   - There is increase plasmid and chromosomally mediated resistance to all the 3 drugs
   - The dose should give serum level 3 times > the minimum inhibitory concentration for > 8 h in tropics

3- **Test for cure** 3-5 days after treatment

4- Treatment of **contacts**
   - Within 2-4 weeks of onset of symptoms or
   - Diagnosis of asymptomatic patients

Chlamydial infections

Causative organism

1- **C. trachomatis** → gram –ve bacterium

2- Very similar to gonoc. Infections

3- Cause less severe symptoms, but leads to more serious sequalae

Clinical features

1- **In males**

- It causes uretheritis and epididymo-orchitis
- Stricture can occur later

2- **In females**

- It leads to cervicitis, mucopurulent discharge and endometritis
- Salpingitis can occur as a sequalae
- Infected females may give in 30% of cases self limiting conjunctivitis in the `1st 2 weeks of life
- Small no. of infected infants develop pneumonitis between age of 6 weeks to 3 months with total IgG, IgM and mild eosinophilia

Diagnosis

1- Urethral swab from males and endocervix of females or 1st catch urine specimen

2- Isolation and tissue culture

3- Direct immunoflurescence

Treatment

1- Tetracycline and erythromycin

2- Azithromycin

Vulvovaginal candidiasis

Etiology

1- Cause is **candida albicans**

2- Isolated from 50% of vagina of sexually active females

3- The source of infection also from GIT

4- Majority of cases are asymptomatic, symptoms appear due to increase no. of yeasts in the vagina

5- **Predisposing factors**

- Pregnancy
- Antibiotics
- Oral contraceptive use
- Immunosuppression
- Increase perineal moisturing (clothes)

Clinical features

1- Pruritis vulvae

2- Vaginal discharge which is white with adherent crude like plaques

3- May be erythema or edema of valvae and vagina

Diagnosis

A wet preparation from vaginal discharge with addition of 10% K hydroxide → Mycelia

Treatment

1- Nystatin

2- Miconazole

Trichomoniasis

Clinical features

1- **In males**

- Most infections are asymptomatic and giving self limiting urethritis

2- **In females**

- 75% complaining of vaginal discharge, pruritis, dysuria, dyspareunia, erythema and punctuate he

Diagnosis

1- Wet preparation from the post-fornix → increase PMNLs and motile flagellated parasite

2- Direct microscopy is less sensitive

3- Culture

Treatment

1- Metronidazole

2- Clotrimazole (less effective)

Bacterial vaginosis

Clinical features

1- Characterized with **malodored vaginal discharge** with change of vaginal bacterial flora (there is increase anaerobes)

2- **The discharge** is white with increase PH > 4.5, fishy smell esp. after addition of 1 drop of 10% K-hydroxide to the discharge

3- It is present in sexually inexperienced females as well as sexually active females

Diagnosis

Presence of **clue cells** in wet preparation or gram stain → it is squamous epithelial cells which are covered with many adherent bacteria

Treatment → metronidazole

Chancroid or soft sore

Incidence

1- Causes 60% of genital ulcers

2- Commoner in uncircumcised and increase risks of transmission of HIV

3- Common in نيروبى وشمال أمريكا

Cause → Haemophylis ducreyi (anaerobic gram –ve bacillus)

Clinical features

1- Incubation period → 3-7 days

2- **A papule** which soon ulcerate

3- **The ulcer**

- Commonly multiple
- Soft
- Painful
- Purulent base
- Bleeds on contact
- Commonly with painful inguinal L.N.

Differential diagnosis

1- 1ry syphilis

2- Herpes simplex

3- Donovanosis

Diagnosis

1- Swab from ulcer base or undermined edge & isolation of H. ducreyi & culture on enriched media

2- Enzyme immunoassay

Treatment

1- Ulcer should be dry and clean

2- **Clotrimoxazole or erythromycin** orally for 7 days

3- **For resistant strains**

- Ciprofloxacin 500 mg daily for 3 days
- Ceftriaxone 500 mg I.M. single dose

Syphilis

Pathogenesis

1- Causative organism

- T. pallidum which is a spirochaete, spiral organism, visible by light microscopy with dark field illumination and can grow on artificial media
- It can't be distinguished from T. pertenui and Carateum which are responsible for Yaws and Pinta

2- Lesions

- The 1ry lesion is controlled by immune system
- The 2ry lesions appear some weeks later due to dissemination of organism and circulating immune complexes, the main pathology in this stage is due to immune complex, the organism can survive in the body for many years
- The tertiary lesions are characterized by small no. of organisms and lymphatic response ending to endarteritis

Clinical features

1- Incubation period → 10-70 days (21 days)

2- 1ry stage [Chancre]

- Develop at the site of inoculation
- Painless indurated with clean base and raised edge
- Does not bleed on contact
- Usually single
- Site
    - In males → on the glans or the shaft of the penis
    - In females → on cervix or vulva
- Usually associated with inguinal lymphadenopathy which are hard and painless
- Resolves spontaneously over several weeks

3- **The 2ry stage [Condyloma lata]**

- The 2ry stage develop after disappearance of chance between 3-6 months
- Popular, macular or pustular rash which desquamates
- In moist areas (axillae and perineum), condyloma lata develop
    - Soft and raised appear
    - Not itching
    - On palm, sole, mm affection in the form of mucus patches or oral ulceration
- May be generalized L.N, nephritis, hepatitis, meningitis, uveitis with fever and malaise
- 2ry syphilis resolve after several weeks, but relapse may occur

4- **Tertiary stage**

- Gumma → painless ulcer with little or no inflammation
- C.V lesions
    - Aortitis, aortic valve incompetence or coronary occlusion
    - May occur after 1st 15 years of illness
- Neurological manifestations
    - Tabes dorsalis and general paresis
    - May occur after 15-20 or 30 years of illness

Diagnosis

1- **Dark field microscopy** from fluid (ulcer but may be –ve in case of antibiotic and antiseptic intake)

2- **Serology**

- Regain tests
    - For monitoring the response to treatment as they give a titre
    - False +ve results may occur in case of chronic infections (rapid plasma regain)
- The treponemal tests
    - They remain +ve for life

- Can't differentiate between current and past infection
- More specific than regain tests
- Can't distinguish between sexually acquired or endemic treponemal infections (T.P. Haemoagglutination and Fluorescent treponemal antibody tests)

- In neonates [IgM by FIA test]
  - Differentiate between true infection and passively acquired maternal antibody

Treatment

1- Recommended treatment regimens

Stage	Treatment	Alternative regimen
Early primary	**Benzathin PCN G** 2.4 million units IM x 1	If PCN allergic: **Doxycycline** 100 mg PO bid x 14 day or **Tetracycline** 500 mg PO 4 times daily x 14 days
Early secondary	Same	Same
Early latent < 1 y	Same	Same
Late latent > 1y or unknown	**Benzathin PCN G** 2.4 million units IM x 3 doses at 1 wk intervals	If PCN allergic: **Doxycycline** 100 mg PO bid x 28 days or **Tetracycline** 500 mg PO 4 times daily x 28 days
Teriary	**Benzathin PCN G** 2.4 million units IM x 3 doses at 1 wk intervals Some experts recommend treating cardiovascular syphilis with **IV PCN**	If PCN allergic: **Doxycycline** 100 mg PO bid x 28 days
Neurosyphilis	**Aqueous crystalline PCN G** 3-4 mu IV q4h x 10-14 days	If compliance ensured: **Procaine PCN** 2.4 mu IM qd **+ probenecid** 500 mg PO 4 times daily x 10-14 days
Pregnancy	**PCN** is the only recommended treatment – desensitize if necessary	

2- **Congenital syphilis**

- Procaine penicillin 50,000 unit/kg I.M. daily for 10 days or
- Benzathin penicillin 50,000 unit/kg/10 days

3- **Treatment of contact (partners)**

- Should be treated if they had sexual contact with the patient up to 3 months prior to symptom onset

4- **Jarisch-Herxheimer reaction**

- Fever, headaches and myalgias common within 24 h posttreatment (affecting up to 90% of patients treated with penicillin for early syphilis and up to 25% during later stages)
- Antipyretics used to alleviate symptoms

Lymphogranuloma venereum

Etiology

1- Causative organism → invasive L1, L2, L3 strain of **C.Trachomatis**

2- Common in males than females

3- Distribution → أثيوبيا ونيجيريا

4- Other names → Climatic bubo, Nicolas-Favre disease

Clinical features

1- Incubation period → 3 – 30 days

2- If sexually active adult presenting with **an inguinal bubo** with no genital ulcer → LGV is an important diagnosis

3- **1st phase**

- Asymptomatic infection of the urethra and cervix or
- Small, painless, herpetiform ulcer which pass unrecognized

4- **2nd phase**

- Painful lymphangitis and lymphadenitis with fever and malaise
- Mostly bilateral nodes which coalesce & become matted projecting above or below the inguinal ligament

- The nodes may rupture and leads to sinuses
- Untreated cases → lymphatic damage leading to elephantiasis of genitalia

5- **In women and homosexual** → acute proctocolitis which lead to abscess, fibrosis and rectal stricture

6- **In premenopausal females** → vulval carcinoma is recorded

Diagnosis

1- **Isolation** and identification of L1-3 strain

2- **CFT** (titre: 1/64) or **microimmunuofluorescent test** (titre: 1/512)

3- Leucocytosis, ↑ SR and IgG cryoglobulins

4- **Biopsy** → stellate abscess is suggestive

5- **Immunofluoreescence** → presence of chlamydial elementary bodies in tissue or discharge is suggestive

Treatment

1- Doxycycline 100 mg PO bid for 3 weeks or

2- Erythromycin base 500 mg PO qid for 3 weeks

3- Plastic surgical operation → ext. elephantiasis

4- Drainage of large flactuant buboes

Donovanosis (granuloma inguinale)

Etiology

1- **Causative organism**

- Calymmatobacterium granulomatis → Capsulated intracellular gram – ve coccobacilli

2- It is common in low socioeconomic conditions and may occurs in epidemics

3- It forms **16% of males genital ulcers**

4- The risk of transmission to partners is lower than for other STD

5- Distribution → الهند, البرازيل وجنوب افريقيا

Clinical features

1- Incubation period → 3-40 days

2- **Small papule** → rupture → granulomatous lesion

3- **Granulomatous lesion**

- Painless
- Beefy red
- Bleeds easily
- Elevated above the surrounding skin

4- **Untreated ulcers** extend along skin folds to the groin and anus

5- **Extragenital lesions**

- Hard masses and abscesses of the neck, mouth, cervix, uterus and ovaries
- Rarely → spread to lung, liver, spleen and bone

6- Elephantiasis and sq. carcinoma may occur

Diagnosis

Biopsy → material or smear stained by silver or Giemsa stain show intracellular Donovan bodies with bipolar densities

Treatment

1- Tetracycline, erythromycin, norfloxacin and lincomycin for 3 weeks

2- Combination between erythromycin and lincomycin for longer time after recovery to prevent relapse

Genital herpes

Causative organism → H. simplex type 2 and less commonly type 1

Clinical features

1- **Localized clusters of vesicles**

- Affects external genitalia, nearby skin urethra, cervix, pharynx and rectum
- The vesicles break and forms ulcers
- There is tender lymphadenopathy

2- **1ry attack is severe** and extends from peripheral nerves to local ganglion

Complications

1- **Sacral radiculopathy** leading to
   - Constipation
   - Retention of urine
   - Shooting pain along legs
2- **Aseptic meningitis**
3- **Premature labor & 60% mortality** rate

Diagnosis

1- Clinically
2- Viral isolation
3- Kits for antigen detection is available

Differential diagnosis

1- Behcet's disease
2- Crohn's disease

Treatment

1- Keep lesion clean and dry
2- Acyclovir and immunosuppression in disseminated lesions & neonates

Genital warts

Causative organism

1- **Human papilloma virus**
2- The most common viral STD, commoner than herpes
3- Types → HPV 6, 11, 16, type 26 which is associated with cancer cervix

Clinical features

1- Soft fleshy vascular **condylomata acuminata** popular warts
2- It may occur in the urethra
3- In pregnant females and immunosuppressed the warts grow more rapidly

Diagnosis

1- Biopsy or cervical cytology
2- Subclinical infection can be detected by PCR

Treatment

1- Application of trichloroacetic acid and 20% podophyllin once or twice weekly

2- **Cryotherapy or diathermy** → for larger warts

3- **Recently**

- 5-fluorouracil ointment
- Podophyllo toxin
- Carbon dioxide laser treatment

Tropical ulcer

Definition

1- A term used to describe **ulcers of the ankle and lower leg** occurring in the tropics and subtropics that are not typical of other leg ulcers of more definitive aetiology (e.g. Buruli ulcers, diabetes and leprosy)

2- Tropical ulcer has been described as a **disease of the poor and hungry**

Etiology

1- There is **no single** agreed causative organism

2- Although, **early lesions** may be infected by

- Bacillus fusiformis
- Anaerobes
- Spirochaetes

3- **Later**, may be infected by

- Staphylococci
- Streptococci

Clinical features

1- **Risk factors**

- Poor nutrition
- Often initiated by minor trauma

2- **Characters**

- Site → below the knee, usually around the ankle
- Typically painful (unlike buruli ulcer)
- Once developed, the ulcer may become chronic and stable, esp. if poorly treated (may be up to 50 yr)
- It can run a destructive course with
    - Deep tissue invasion
    - Osteitis
    - Risk of amputation

Complications

1- **Recurrent ulceration**
   - May occur in the same site when a 'paper-thin' scar forms over the ulcer

2- **Squamous cell carcinoma**
   - May occasionally develop, usually in very chronic cases, and at the edge of the ulcer

3- **Tetanus**

Treatment

1- Good **nutrition and vitamin** supplementation

2- **Antibiotics**
   - Should be given in adequate dosages
   - For early ulcers → penicillin is usually sufficient
   - Later → other broad spectrum antibiotics may be needed

3- **Dressings**
   - Must be non-adherent (e.g. saline soaks and petroleum jelly impregnated gauze) → otherwise they will stick to the ulcer surface and when removed they will disrupt granulation tissue
   - For sloughy ulcers → honey, sugar paste or paw paw (papaya) are useful inexpensive dressings

4- **Surgery**
   - Curettage and debridement under general anaesthetic → may be required for large infected ulcers
   - Skin grafting → may be helpful
   - Skin grafting → may be helpful

Prevention

1- Trauma avoidance is important [wearing adequate footwear]

2- Prompt and adequate treatment of ankle and leg skin breaks

3- Good health and nutrition

Dermatological presentations in the tropics

Skin itching

1- **Scabies** → typical distribution but burrows often masked by 2ry infection

2- **Insect bites** → popular urticaria on exposed surfaces

3- **Superficial fungal infection**

- Examine scrapings for hyphae after clearing in 10% K hydroxide

4- **Eczema**

- Often a personal or family history of allergy
- Or recent exposure to drugs or topical sensitizer

5- **Onchocerciasis**

- Geographical distribution
- Examine for nodules and take skin snips

6- **Perianal itching**

- Enterobius vermicularis
- T saginata

Creeping eruptions

1- **Cutaneous larva migrans**

- From dog hookworms
- Slowely extending persistent itching track most often on the foot or lower leg
- Multiple infections cause severe itching

2- **Larva currens**

- Caused by migrating strongyloides larvae
- Urticaria like rapidly moving tracks found between the neck and the knees and last for hours or a day or two only

3- **Track like lesions**

- From larvae of some species of paragonimus, Gnathostoma spinigerum or from some fly larvae are less common

Papules

1- Milia
2- Onchocerciasis
3- HIV related
4- Scabies
5- Insect bites
6- Acne
7- Cercarial dermatitis
8- Tungiasis

Urticaria

1- Popular urticaria from **insect bites**

2- **Katayama syndrome** in schistosomiasis

- Follows fresh water exposure by days to months
- Associated with cough, wheeze and marked eosinophilia

3- **Intestinal helminthes**

- Round worms
- Hookworms
- Migrating larvae of strongyloides

4- **Filarial infection**

5- Drugs as penicillin and sulfa

6- Food additives

7- Jellyfish stings or other envenomation

8- Contact with plants

Petechial rashes

1- **Meningococcal septicemia**

2- **Dengue and dengue haemorrhagic fever**

3- **Viral haemorrhagic fever**

- Including Lassa, Ebola and Crimean Congo

4- Chikungunya infection

5- Vasculitis including HSP

6- DIC

7- Infective endocarditis

Bullae

1- **Bullous impetigo**

2- **Insect bites**

3- Sunburn

4- Burns and scalds

5- Drug eruptions

6- Snake bite and other causes of envenoming

7- **Larva migrans**

8- Pemphigus including Brazilian pemphigus foliaceous

9- Porphyria associated with sun exposure

Hypopigmented macules

1- Postinflammation and scarring

2- Pityriasis versicolor → Raindrop patches over trunk with slight scaling

3- **Leprosy** → loss of sensation and enlarged nerves

4- Onchocerciasis → patches chiefly over shins; nodules and +ve skin snips

5- Yaws → mainly affects palms and soles; +ve syphilis serology

6- Vitiligo

- Usually white sometimes hyperpigmented borders
- Symmetrical; association with autoimmune disease

7- Post kala azar dermal leishmaniasis

Hyperpigmentation

1- Pellagra affects sun exposed skin

2- Pregnancy

3- Chronic arsenic poisoning

- Slaty grey colour of trunk with small areas of normal skin
- Hyperkeratosis of palms and soles

4- Addison's disease → look for pigment in oral mucosa

5- Hypertrophic lichen planus

- Warty patches typically involving calves, forearms and lower back

6- Kaposi's sarcoma

Skin nodules

1- Furuncle

2- Furuncular myiasis

3- Leprosy

- The nodules are frequently over the ears, eyebrows and face
- The diagnosis is confirmed by slit skin smears for acid fast bacilli

4- Erythema nodosum

- Resulting from leprosy is sometimes widespread on the body
- Streptococcal infection, sarcoidosis and TB are other causes

5- Leishmaniasis

- Single or multiple nodules may take months to ulcerate
- Predominant on exposed surfaces but spread along lymphatics also occurs
- Diffuse cutaneous leishmaniasis and post kala azar dermal leishmaniasis can resemble nodular leprosy

6- Kaposi's sarcoma

- Chiefly affecting limbs of older persons in endemic areas
- But any skin surface and mucosae often with lymph node enlargement in AIDS

7- Fungal infections

- Including chromoblastomycosis, sporotrichosis, histoplasma capsulatum and H. duboisii, paracoccidiodes brasiliensis, penicillium marneffei
- Some are particularly common as 2ry infections in the immunosuppressed

8- Onchoerciasis → subcutaneous nodules

9- Cysticercosis

10- Juxta articular nodules are found in late yaws

11- Non tropical causes

- Rheumatoid nodules
- Gouty tophi
- Neurofibromata

Skin ulcers

1- <u>Acute ulcers</u> (heal quickly)

- Trauma
- Insect bites

2- <u>Chronic ulcers in temperate climate</u>

- Diabetic ulcer
- Venous and arterial ulcers

  Less common in most young tropical populations

3- <u>Chronic ulcers in tropics</u>

Type of ulcer	Main characteristics	Diagnosis
Tropical ulcer	Painful, rapid onset, usually lower leg	Heals on non-specific regimen
Buruli ulcer	Extensive, mainly painless; very deep undermined edges	Finding acid fast bacilli in edge of ulcer
Cutaneous leishmaniasis	Single or multiple, often with infiltrated edges, not undermined	Amastigotes in edges of lesions. Culture or PCR
Desert sore, veld sore (cutaneous diphtheria)	Usually single, painful onset with vesicle, adherent slough, undermined, paralysis from toxin	Culture, as well as the clinical combination of ulcer with neurological deficit
Tertiary syphilis (gumma)	Chronic, usually painless ulcers on extremity	Serological tests for syphilis. Spirochaetes cannot be found
Tuberculous ulcer	Frank ulcers often follow SC TB; there may be adjacent cold abscess or evidence of TB elsewhere	Microscopy for AAFB (acid and alcohol fast bacilli). Culture
Sickle cell disease in adults	Rare in Africa where few adults with the disease survive. Ulcers often symmetrical on lower legs	Patient obviously anemic and sickling test positive
Dracunculiasis	The pearly prolapsed uterus is seen early	By identifying the worm or larvae expelled after exposure to water
Trophic ulcer of leprosy	Painless; may be deeply penetrating on the sole	Associated evidence of nerve damage: thick nerves, loss of sensation
Diabetic ulcer	In the tropics usually neuropathic. On soles of feet over bony prominences. Usually painless	Evidence of neuropathy. Known or newly diagnosed diabetes
Malignant ulcer	Squamous cell carcinoma usually	Biopsy and histology
Mycoses (subcutaneous or deep)	Usually ulcerates within a performed granulomatous nodule	Biopsy, culture and histology. Microscopy for hyphae and spores

Buruli ulcer

Definition

1- It is a **highly destructive ulcerating condition** caused by Mycobacterium ulcerans

2- Any part of the body may be affected esp. areas exposed to minor trauma such as **the limbs**

3- M.ulcerans ranks 3rd among mycobacterial infections affecting immunocompetent humans

Etiology and pathogenesis

1- **M.ulcerans** → Slowly growing acid and alcohol fast organism

2- **Mode of infection**

- Penetrating injury (usually minor) resulting in inoculation of the organism which is found naturally in soil or stagnant water
- May also follow the bite of an infected water bug
- Person to person transmission is very rare

3- **Pathogenesis**

- Mycolactones - soluble polyketide toxins causes
  - Local immune-suppression
  - Ulceration
  - Necrosis
  - Painlessness characteristic of uncomplicated lesions
- Intercurrent helmintic infections → also predispose to ulceration

4- **Distribution**

- Several parts of Africa esp. the **Buruli region of Uganda**, Ghana, Papua New Guinea, the Americas, South East Asia and China
- Among koala bears and Australian golfers

Clinical features

1- **Age** → predominantly a disease of children

2- **Four non ulcerative presentations** usually precedes ulceration

- Papule → painless, sometimes itchy, non tender palpable intradermal lesion (seen in Australia but rare in Africa)
- Nodule → painless palpable firm lesion, 1-2 cm in diameter, situated in the subcutaneous tissue and usually attached to the skin (uncommon in Australia)
- Plaque → painless well demarcated, elevated, dry indurated lesion > 2 cm
- Oedematous → diffuse extensive non pitting swelling, ill defined margin, firm, usually painful with or without colour changes over the affected skin

3- The ulcer

- With time, the overlying skin breaks down and an ulcer forms with a necrotic centre, often spreading very rapidly in all directions
- The following features are very characteristic

  - The ulcer usually painless, a factor contributing to the delay in health care seeking behaviour
  - The skin at the edge of the ulcer is deeply undermined
  - Satellite ulcers often communicate with the original ulcer by a subcutaneous tunnel, so the skin between adjacent ulcers is often unattached to the underlying tissues. The extent of the damage is always much greater than it looks from the surface

4- Regional adenitis and systemic symptoms

- Unusually and if present are suggestive of 1ry or 2ry bacterial infection

5- Complications

- Tetanus
- 1ry or 2ry osteomyelitis
- After months or years, healing may result in scarring, ankylosis and contractures

- 25% complicated by amputation or loss of sight
- HIV not associated with altered clinical course

Differential diagnosis

Papule	- **Granuloma annulare** - Herpes - Insect bites - Leishmania - Pimple - Pityriasis - Psoriasis
Nodule	- **Boil** - Cyst - Leishmaniasis - Lipoma - Lymphadenitis - Mycosis - Onchocercoma
Plaque	- **Cellulitis** - Hematoma - Insect bites - Leishmaniasis - Leprosy - Mycosis - Psoriasis
Oedema	- **Actinomycosis** - Cellulitis - Elephantiasis - Necrotizing fasciitis - Onchoercoma - Osteomyelitis
Ulcer	- **Cutaneous diphtheria** - Guinea worm - Leishmaniasis - Necrotizing fasciitis - Neurogenic ulcer - Tropical ulcer - Tuberculosis - Sickle cell disease - Squamous cell carcinoma - Syphilis - Venous ulcer - Yaws

Investigations

1- **The slough from the edge of the ulcer**
   - Usually contains numerous acid fast bacilli on Z.N stain but may be negative

2- **Culture** → gives too much false +ve results

3- **PCR** → now used in diagnosis

Treatment

1- **Small pre ulcerative lesions**
   - Surgical excision

2- **Necrotic ulcer**
   - Should be excised with care to remove all affected tissue by extending the margin into healthy tissue
   - Followed by primary closure or split skin grafting

3- **Patients with contractures**
   - May require surgery or physiotherapy

4- **Antibiotic treatment**
   - Regimen
     - Rifampicin 10mg/kg +
     - Streptomycin 15mg/kg i.m. daily for 8 weeks
   - Cure rate
     - Drugs + surgery → 96%
     - Drugs without surgery → 47%
   - Effect
     - Reduce ulcer size
     - Makes larger ulcers more amenable to surgery and grafting
   - Most successful in
     - Patients with nodules, papules and plaques
     - Ulcers < 5 cm
   - Recurrence → < 2% overall

5- **Topical treatment**

- Nitric oxide, phenytoin powder or local heat treatment
- This treatment has been used successfully in treatment esp. smaller lesions

Acute flaccid paralysis

Causes

1- **Poliomyelitis**.

2- Enterovirus 71.

3- Japanese encephalitis & West Nile viruses.

4- **Guillain-Barre syndrome** (polyneuropathy typically presenting weeks after febrile illness).

5- Chinese paralytic syndrome:

- Acute motor & axonal neuropathy "AMAN" typically follows diarrhea caused by Campylobacter jejuni.
- It occurs in summer epidemics in China.

6- **Other causes**

- Paralytic rabies.
- Botulinum toxin.
- Tick paralysis

Spastic paralysis

Causes

1- **Tuberculosis** (i.e. Pott's disease).

2- HIV myelopathy.

3- Tropical spastic paraparesis:

- It's found in equatorial Africa, South America, Caribbean, and Japan.
- Caused by human T-lymphotropic virus type 1 (HTLV-1), transmitted sexually, by exposure to blood products or by breast milk.

4- Subacute combined degeneration of spinal cord (caused by Vit B12 deficiency caused by D. latum).

5- **Transverse myelitis**: can be associated with common infectious agents including

- Viral → HIV, Dengue.
- Bacterial → Mycoplasma pneumonia.
- Spirocetal → Borrelia burgdorferi, leptospirosis, syphilis.
- Rickettsial → scrub typhus.

Environmental health hazards

Snake bite

Clinical features

1- Local effects

- Pain, swelling or blistering of the bitten limb
- Necrosis at the site of the wound can sometimes develop

2- Systemic effects

- Non specific symptoms: vomiting, headache and collapse
- Painful regional lymphadenopathy indicating absorption of venom
- Specific signs
  - Non-clotting blood
  - Bleeding from gums, old wounds and sores
  - Neurotoxicity → ptosis, bulbar palsy and respiratory paralysis
  - Rhabdomyolysis and muscle pains and black urine
  - Shock; hypotension, usually resulting from hypovolaemia

3- Manifestations of various types

- Vipers
  - Commonly cause local swelling, shock, bleeding and non-clotting blood
- Elapids
  - Cause neurotoxicity
  - Usually minimal signs at the bite site (with the exception of some cobras which also cause necrosis)
- Sea snakes
  - Cause myotoxicity and subsequent paresis
- Exceptions
  - Some vipers cause neurotoxicity
  - Australian elapids also cause non-clotting blood and haemorrhage

First aid for snakebites

1- **Reassure the patient**. Many symptoms following snakebite are caused by anxiety
2- **Immobilize the limb**. Moving the limb may increase systemic absorption of venom (Splinting is especially helpful in children)
3- **Avoid harmful maneuvers** such as cutting, suction or tourniquets
4- **Consider a pressure bandage** in regions where snakebite does not cause tissue necrosis
    - Esp. if rapid transport to hospital is not possible
    - Esp. important for snakes that cause neurotoxicity
    - A firm crepe bandage should be applied over the bite site and wound up the limb
5- Transport to hospital as soon as possible
6- If the snake has been killed, take it to hospital with the patient

Diagnosis and initial treatment

1- **Think** of envenoming in unusual cases
2- Carefully **examine** bitten limb for local signs
3- **Measure** the pulse, respiratory rate, blood pressure and urine output. The blood pressure must be watched if patients are unwell, bleeding or have significant swelling; shock is common in viper bites
4- **Look for non-clotting blood**
    - This may be the only sign of envenoming in some viper bites
    - The 20-min whole blood clotting test is an extremely easy and useful test
    - This should be performed on admission and repeated 6h later

> - Place a few milliliters of freshly sampled blood in a new, clean, dry glass tube or bottle
> - Leave undisturbed for 20min at ambient temperature
> - Tip the vessel once

- If the blood is still liquid (unclotted) and runs out, the patient has hypofibrinogenaemia (incoagulable blood) as a result of venom-induced consumption coagulopathy

5- **Look carefully for signs of bleeding** which may be subtle (gums/old wounds/sores). Bleeding internally (most often intracranial) may cause clinical signs

6- **Look for early signs of neurotoxicity:**
   - Ptosis which may be interpreted as feeling sleepy
   - Limb weakness
   - Difficulties in talking, swallowing or breathing

7- **Check for muscle tenderness and myoglobinuria** in sea snake bites

8- **Take blood for**
   - Hb, TLC, and platelet count
   - PT, PTT and fibrinogen levels if available
   - Serum urea and creatinine
   - Creatine phosphokinase reflecting skeletal muscle damage

9- **Take ECG** if available

Management

1- **General measures**
   - All patients should be observed in hospital for 12-24 h, even if there are no signs of envenoming initially
   - They should be regularly reviewed as envenoming can develop rapidly
   - Nurse patients on their side with a slight head down tilt to prevent aspiration of blood or secretions
   - Avoid I.M. injections and invasive procedures in patients with incoagulable blood
   - Tetanus prophylaxis should be given
   - Routine antibiotic prophylaxis is not required unless necrosis is present

2- Antivenom

- Indications
  - Signs of systemic envenoming
  - Evidence for its efficacy in severe local envenoming is poor, but it is usually indicated if swelling extends over more than half the bitten limb
- Types
  - Monospecific (monovalent) antivenom → can be used for a single species of snake
  - Polyspecific (polyvalent) → for a number of different species
- The choice and dose
  - Depends upon manufacturers recommendations and local experience
  - Children require exactly the same dose as adults, as the dose is dependent upon amount of venom injected and not body weight
- Administration and precautions
  - Antivenom should be diluted in 2-3 volumes of dextrose/saline and infused over an hour or so. The infusion rate should be slow initially and gradually increased
  - Adrenaline should be drawn up in a syringe ready for use. Routine prophylaxis against antivenom reactions is currently unproven and should not generally be used
  - Patients should be observed closely during antivenom administration. Common early signs of an antivenom reaction are urticaria, itching, restlessness, fever, cough or feeling of constriction in the throat
  - Patients with these signs should be treated with adrenaline (0.01mg/kg) I.M. An antihistamine, for example chlorphenamine (0.2mg/kg i.m. or i.v.) should also be given
  - Unless life threatening anaphylaxis has occurred, antivenom can cautiously be restarted after this treatment

- Response to antivenom should be monitored
    - In the presence of coagulopathy, restoration of clotting depends upon hepatic resynthesis of clotting factors
    - The WBCT20 should be repeated 6 h after antivenom, if blood is still non-clotting, further antivenom is indicated
    - After restoration of coagulation, measurement of WBCT20 should be repeated every 6 h as a coagulopathy may recur because of late absorption of venom from the bite site
    - The response of neurotoxicity to antivenom is less predictable.
    - In species with predominantly postsynaptically acting toxins, antivenom may reverse neurotoxicity; failure to do so is an indication for further doses
    - However, response to antivenom is poor in species with presynaptically acting toxins

3- Other therapy

- Surgery
    - Sloughs from necrotic wounds should be excised
    - Skin grafting may be necessary
    - Severe swelling may lead to a suspicion of compartment syndrome
    - Fasciotomy should not be performed unless there is definite evidence of raised intracompartmental pressure (>45 mmHg) and any coagulopathy has been corrected
- Blood products
    - Not necessary to treat a coagulopathy if adequate antivenom has been given
- Endotracheal intubation
    - Should be performed to prevent aspiration if bulbar palsy develops, often obvious when difficulty in swallowing leads to pooling of secretions

- Artificial ventilation
    - Required if paralysis of intercostal muscles and diaphragm is present
    - Can be performed by manual bagging and may need to be maintained for days using relays of relatives if necessary
- Anticholinesterases
    - May reverse neurotoxicity following envenoming by some species with postsynaptic toxins
- Careful fluid balance
    - Should be maintained to treat shock and prevent renal failure
- Some cobras spit venom into the eyes of their victims. Rapid irrigation with water will prevent severe inflammation. 0.5% adrenaline drops may help to reduce pain and inflammation

Scorpion stings

Clinical features

1- Locally

- The scorpion sting is extremely painful causing burning sensation around the bite site which may last for many hours or even days (the major feature of envenoming)
- May be inflammation and tissue necrosis

2- Generally

- Systemic envenoming is more common in children and may occur within minutes of a bite
- Major clinical features are caused by activation of the autonomic nervous system
- Severe HTN, myocardial failure and pulmonary edema are particularly prominent in severe envenoming

- Clinical features include

• Tachypnoea - Excessive salivation • Nausea and vomiting • Lachrymation - Sweating • Abdominal pain - Muscle twitches and spasms • Hypertension - Pulmonary edema • Cardiac arrhythmias - Hypotension • Respiratory failure

Management

1- Take the patient to **hospital** immediately; delay is a frequent cause of death

2- Application of **tourniquet** just above the site of bite to decrease the absorption of the toxin

3- **Suction** of the venom very rapidly (incision at the site of the wound may be needed)

4- **Control pain** with infiltration of lidocaine around the wound or systemic opiates (with care)

5- **Scorpion antivenom** is available for some species. It should be given i.v. in systemic envenoming, but i.m. injection has been used with good effect

6- Prazosin is particularly effective for treating **hypertension and cardiac failure**

7- **Severe pulmonary edema** requires aggressive treatment with diuretics and vasodilators

8- Treatment of **shock** if present

9- In severe cases, **corticosteroids** may be needed

Heat disorders

Various heat illneses

Degree	Illness	Thermoregulatory mechanisms
Mild	- Sweat rash - Heat syncope - Heat edema - Heat tetany - Heat cramps هام	Intact
Moderate	Heat exhaustion هام	Intact
Severe	Heat stroke هام	Failed

Precipitating factors

1- **Increase in the atmospheric** temperature and humidity:
   - About 90% of heat stroke occurs when atmospheric temperature increases > 30C

2- **Lack of acclimatization**

3- Fatigue

4- **Physical conditions:**
   - Extremities of age
   - Obesity
   - Alcohol consumption
   - DM
   - Strenuous exercise
   - Cardiovascular diseases
   - Anticholinergic drugs
   - Previous history

Sweat rash

Characters

1- **An erythematous rash** occurs due to excessive sweating
2- It is burning and itchy in character
3- It covers the body especially in the flexure points
4- **Mechanism**:it is claimed that sweating leads to swelling of the keratinocytes surrounding the opening of the sweat glands causing its obstruction and initiating inflammatory reaction

Treatment

1- Take the patient to a **cold place**
2- Application of **soothing lotions** like calamine lotion

Heat syncope

Characters

1- It occurs after standing for long time in hot weather
2- Characterized by **sudden falling** of the person on the ground
3- **Mechanism**: excessive VD of the peripheral blood vessels as a result of exposure to heat → pooling of the blood to the periphery while small amount of blood reaches the brain

Treatment → take the patient to cold place

Heat tetany

Mechanism

1- It is due to respiratory alkalosis that may occurs secondary to hypercapnia leading to **precipitation of ionized calcium**
2- It is a reversible condition

Treatment → taking the patient to cold place

Heat cramps

Etiology

1- **Mechanism**: most probably due to salt and water depletion

2- It results from excessive sweating following drinking of excessive amounts of **unsalted water**

3- During sweating the body losses water and sodium chloride leading to electrolyte imbalance and neuromuscular irritability with cramps

4- The disease occurs in hot weather but **muscular activity** is essential in order to induce excessive sweating

Characters

1- Contraction of one muscle without relaxation of the opposite one

2- Usually affects the **calf muscles** and then may spread to affect other muscles

3- Usually occurs after some period following exercise

4- Cramps are **extremely painful** of short duration and in-between, the muscles are relaxed but they may persist for several hours

5- Rectal and skin temp. and B.p usually normal but pulse is rapid

Treatment

1- Putting the patient in a cool place and acclimatization

2- Bed rest

3- **Replacement** of salt and water depletion:

- 1 liter of saline in 1-3 hours is usually enough or oral water and salt

Heat exhaustion

Mechanism

1- **Due to water and salt loss**

2- Occur usually when **non-acclimatized persons** kept for long time in hot humid weather with continuous sweating even if no physical exercise is done

- Rapid course → predominant water loss
- Gradual course → predominant salt loss

Symptoms

1- Headache

2- Anorexia, nausea and vomiting

3- **Giddiness**

4- Excessive thirst

5- Cramps may occur

Signs

1- **Profuse sweating**

2- **Flushing**

3- Temperature is normal or between 38-39C

4- Signs of dehydration

- Hypotension, tachycadrdia, sunken eyes and inelastic skin

5- Mental changes which denotes that the condition is shifted to heat stroke

Laboratory analysis

1- ↑ hematocrite value

2- ↑ sodium level (relative)

3- ↑ hepatic enzymes

4- ↑ creatinine kinase level

5- Decreased glucose level

Treatment

1- Put the patient in dry cool place

2- **Replace the water and salt loss** according to the degree of dehydration

3- **Dextrose 5% in 1/2 normal saline** is the usuall fluids needed

- The patient may needs up to 4 liters over 6-8 hours especially in physically fit young patient
- In elderly, the replacement should be gradual

Heat stroke or hyperpyrexia

Definition and facts

1- **It is a failure of thermoregulatory mechanisms** due to hot wet weather leading to increase in body temperature to a lethal level > 40.6 C causing a wide spread cellular damage

2- **It is a medical emergency** of high mortality rate **characterized** by
   - Rectal temp. > 40 C
   - Hot dry skin
   - Disturbance of consciousness (comatose or semicomatose or delirious) ± convulsions

3- **At about 32.5 degree**, sweating starts to share in the mechanisms of heat loss and at 35 degree, sweating and evaporation of the sweat becomes the main mechanism for heat loss

4- **Under normal conditions:**
   - Stimuli pass to the hypothalamus to stimulate the heat regulating center which sends impulses to the sweat glands and in this way, sweating occurs which helps heat loss through evaporation

5- **In heat stroke:**
   - The heat regulating center is damaged and so no impulses go to the sweat glands and no heat can be lost by evaporation and so the body temp. will rise

6- **To decrease body temperature**
   - Sweating [healthy sweat glands + intact innervations]
   - Evaporation [dry air + air current]

Predisposing factors

1- **Environmental factors**
   - Exposure to hot humid weather with decreased air current (when humidity reaches 75%, evaporation of the sweat nearly ceases)
   - Acclimatization

- Sudden exposure of non acclimatized person to hot humid atmosphere for 48 hours or more can cause heat stroke

- Epidemic heat stroke
  - Occurs when a city experienced a cold winter followed by a hot humid weather in the late spring or early summer
- Wearing heavy clothes in a hot atmosphere
- Military personnels, miners, athletes, labors and young people doing exercise or hard work in hot humid weather is liable to develop exertional type of heat stroke
- Cases of heat stroke are reported following Turkish baths or saunas

2- Age:

- Children and elderly is the most vulnerable group

3- Obesity

- Fat layer work as insolator for heat loss

4- Chronic illness

- Cardiovascular diseases
- DM
- Hemi or quadriplegia with autonomic dysfunction

5- Infection

- Per su rarely cause hyperthermia but may initiate the condition only and the environment completes

6- Dehydration

- Affects the rate of sweating and interface with the heat loss (dehydration fever)

7- Drugs

- Anticholinergic drugs
- Major tranquilizers
- Phenothiazines
- Neuroleptic drugs
- Inhalation anaesthetics

Effects of hyperthermia on the body

1- **Basic changes**

- The lethal effects occur when the body temperature reaches 42 degree but some considered the degree of 41 is a critical level
- The 3 main factors in the etiology of heat stroke are:
  - High body temp.
  - Metabolic acidosis
  - Tissue hypoxia
- Denaturation of proteins, enzymes and hormones with liquefaction of lipids including the brain tissue occurs at 42 degree
- Also, oxidative phosphorylation ceased at this degree with loss of energy sources to different tissues including the heat regulatory centre
- The effects depends on the duration of hyperthermia
- The first cell to be affected is the brain cell

2- **The brain**

- Mental changes, stupor and coma
- Convulsions or decerebrate rigidity
- Quadriplegia, hemiplegia or monoplegia
- Different brain infarctions
- Paralysis of centers like heat regulation center or respiratory center leading to death

3- **The liver**

- Degeneration then necrosis to the liver cells may lead to liver cell failure
- Jaundice and elevated liver enzymes may occur

4- **Kidney**

- Destruction of the renal cells leading to renal failure
- Proteinuria with granular casts and red cells is common

5- **Cardiovascular system**

- Injury to the endothelial lining of the vessels causing DIC (presenting as hemorrhages and purpuras and may be hemoptysis)

- Affection of the conductive system of the heart may lead to different types of arrhythmias and heart failure
- Pulmonary edema is terminal

6- Skeletal muscles

- Destruction of the skeletal muscle cells (rhabdomyolysis) especially in exertional type leading to myoglobinuria with possibility of renal tubular obstruction and renal failure
- Precipitation of Ca and phosphate on the destructed muscle cells leads to hypocalcemia and hypophosphatemia
- Na enters to inside the cells and K goes outside the cells leading to hyperkalemia and hyponatremia

Types of heat stroke

1- Classical type

- Occurs mainly in the extremities of age
- Infants and children may have undeveloped heat regulating center and sweat glands with high metabolic rate
- Old people may have low cardiac reserve, reduced CNS reflexes and may use medications that affect sweating and vasodilatation
- Predisposing illnesses are common
- It occurs during pilgrimage season (epidemic)
- Prolonged heat wave
- Onset is gradual (commonly > 48 hours)
- Dehydration is more due to prolonged sweating
- At presentation, skin is commonly dry (absent sweating)
- Respiratory alkalosis
- Rhabdomyolysis, DIC, hyperuricemia and ARF are rare

2- Exertional type

- Occurs commonly in middle aged healthy persons but can occur at any age

- Occurs in non acclimatized persons during exercise or hard work in hot humid atmosphere
- Occurs sporadically
- No predisposing illnesses
- Variable prevailing weather
- Onset is sudden and acute
- Less dehydration
- Sweating may be present
- Lactic acidosis
- Rhabdomyolysis, DIC, hyperuricemia and ARF are common

Symptoms [occurs prior to coma]

1- **Headache**
2- Nausea ,vomiting and diarrhea are common
3- Unsteadiness
4- Light headedness
5- Piloerection especially over the arms and chest
6- Paraesthesia
7- **Change of behavior and hallucination**
8- Most patients presenting with syncope and **coma**
9- In some cases, **coma is preceded by** short period of confusion, lack of concentration, lethargy and general weakness

Signs

1- **Body temperature**
   - Must be taken rectally, may be > 41 degree
   - May be cold cold extremities due to peripheral circulatory failure
2- **Heart rate**
   - In case of dehydration or heart failure → usually tachycardia with weak pulse
   - In the absence of dehydration → pulse may full
   - In arrhythmia → repound irregular pulse

- In heart block → bradycardia

3- Blood pressure

- May be hypotension due to dehydration or low cardiac output or high output failure (high temperature)

4- Respiratory rate

- Usually deep rapid respiration due to high temp.
- Irregular respiration (Chyne stoke) in the terminal stage
- Bubbling crepitation and frothy sputum in pulmonary edema

5- Skin

- Usually grey and dry
- May be flushed and sweaty
- Petechial hemorrhages and ecchymosis may be present
- Sweat rash is usually present

6- Coma

- With constricted fixed pupils
- ± Convulsions
- Muscle rigidity
- Tremors
- Occulogyric crises or transient hemiplegia may be present

7- Signs of dehydration are usuall

Heat exhaustion	Heat stroke
Moist and clammy skin	Dry hot skin
Dilated pupils	Constricted pupils
Normal or subnormal temperature	Very high body temperature

Diagnostic tests

1- Blood gases

- Commonly reveals metabolic acidosis due to lactate accumulation especially in exertional type
- Respiratory alkalosis may be present due to hypercapnia

2- CBC

- Leucocytosis is common, may reach high levels (35000- 50000/cmm)

3- ALT, AST and LDH

- Markedly elevated
- AST level is prognostic, the level of 1000 iu/L or more in the first 24 hours reflects a poor prognosis with serious brain, liver and renal damage

4- PT, PTT, PC, INR

5- Kidney functions

6- Creatinine kinase (CK)

- Markedly elevated especially in exertional type

7- Myoglobinuria and hyperuricemia

- Usually present due to destruction of muscle fibers

8- Blood glucose level

- Always there is hypoglycemia especially in exertional type and may be severe

9- Electrolytes

- ± Na according to the type of dehydration
- ↑ K in first 24 hours
- ↓ Ca and phosphate

10- ECG

- ST segment and T wave abnormalities with variable arrhythmias and bundle branch block may occur
- Most of these abnormalities are reversible after cooling

Differential diagnosis [Fever+coma]

1- CNS infections

2- Cerebral hemorrhage

3- Cerebral malaria

4- Fulminant viral hepatitis

Management

1- Principles

- Heat stroke is on of the medical emergencies that needs rapid interference
- Rapid and effective cooling is the corner stone of treatment
- The seconds are precious for the patient, so our aim is to decrease the body temperature below the harmful level as quickly as possible to avoid irreversible cellular damage
- With rapid interference, the mortality rate decreased from 80% to 10%

2- Aggressive cooling measures

- Direct application of ice on the whole body
- Immersing the body in cold or iced water
- Application of ice in areas of great vessels passage e.g. axilla, groin and front of the neck
- IV infusion of cold fluids
- Gastric lavage with iced fluids
- Peritoneal lvage with iced fluids
- Inhalation of cold air
- Disadvantages of these methods
    - The cooling rate is less (about 0.1 degree/min) except in peritoneal lavage (0.55 degree/min)
    - Difficult for application in comatosed patient
    - May cause shivering which may increase body temperature
    - Direct ice to the skin leads to VC
    - Ice enema may cause shock and sudden death
    - Peritoneal lavage may leads to peritonitis

3- Slow evaporative technique

- The idea depends on the smooth cooling effect of the evaporation of water

- This is done by spraying the body with warm water or covering it with blanket sulked in warm water then exposes the body to strong current of dry air
- Ice bag must be applied to the head only
- This process continues until the temp. reaches 39 degree and then cooling must be stopped
- Advantages
    - Faster rate of cooling (0.33 degree/min)
    - Easily applied for comatosed patient
    - Not cause shivering or peripheral VC
- This method must be done in a specialized center "The heat stroke center"
- Makkah body cooling unit (MBCU): dissipates the patient's heat by evaboration of a spray of atomized water (at 15 C) by a flow of warm air (at 45 C) .This maintains the skin temp. at the normal level of 30-33 C

4- General status

- Correction of water and electrolyte disturbance and support of vital centers during cooling are essential
- Bleeding diathesis (DIC) should be treated by fresh blood transfusion

5- Prognosis

- Usually, the exertional type in young patients when treated earlier, give rapid response without complications
- Old people with classic type take more time to regain consciousness even with rapid interference

The heat stroke and heat exhaustion center

1- Cooling room

- Enough number of air conditions insure a temperature room 25-30 i.e. 27 and also dry air

- Slated beds without mattresses and opposite to each bed one fan must be fixed to wall to supply a horizontal current of air
- A number of suction fans in the upper part of the wall for renewal of air and removal of humid air
- A source of tape water and ice must be in the cooling room
- All equipments, instruments and emergency drugs needed for comatosed patient must be supplied

2- Observation room

- Is a neighboring conditioned room containing normal beds for observation for 24 hours after cooling

3- Once the patient arrives

- His clothes must be removed quickly and the put on the special bed in the cooling room
- Get IV line and take enough blood sample for CBC, renal and liver function tests, blood gases, electrolytes, glucose, uric acid and bleeding & clotting time
- Urinary catheter must be fixed for collection of urine
- Start IV fluids especially saline then dextrose 5% for correction of dehydration
- In exertional type, 50% dextrose infusion is required as there may be severe hypoglycemia

4- Cooling and evaporation

- Apply ice bag over the head only to the angle of the mandible
- Cover the body with wet blanket or spray the body directly with warm water
- Re-wet the blanket or re-spray the body when becoming dry
- Temp. must be taken rectally every 3 min
- This process must be continued until temp. reaches 39 C then stop cooling and take the patient to the observation with light clothes

5- **Medications**

- Give antipyretic like paracetamol
- Give decadron IV to decrease brain edema and minimize the occurrence of relapse of hyperthermia
- Give valium if there is convulsions

6- **Other measures**

- Search for any infection and treat accordingly
- Do LP if meningitis is suspected
- Correct electrolytes and acid base disturbances
- Dehydration must be corrected gradually in old ages

7- **Discharge**

- If there is no complications and the patient regain consciousness without relapse over 24 hours and no infection you can discharge your patient
- The patient must be informed about his illness and advised to avoid further attacks

Hyperthermia

Definition → it is increase of body temp. > 40.6 degree [elevation of core temperature without elevation of the hypothalamic set point due to inadequate heat dissipation]

Causes

1- **Environmental** → heat stroke

2- **Drug induced**

- Malignant hyperthermia
- Neuroleptic malignant syndrome

3- **Infective**

- Cerebral malaria
- Encephalitis

4- **Endocrinal** → thyrotoxic crises

5- **Miscellaneous**

- Status epilepticus
- Pontine haemorrhage
- Narcotic intoxication
- Serotonin syndrome

Fever

Definition → increase of body temp. > 38 degree

Types

1- **Continuous** → permanent fever

2- **Remitant** → swinging not more than 1 C

3- **Intermittent or hectic** → swinging more than 1 C reaching the base line at least once per 24 hours

4- **Relapsing** → waxes and wanes cyclically

Mechanism

1- **Changing the set point in the anterior hypothalamus**

- By the effect of immune system stimulation through series of reactions [infections, autoimmune reactions, malignancy, drugs,….]
- Bacterial (lipo-polysach. Capsule, endo and exotoxins), viral and parasitic infections → exogenous pyrogens → stimulation of macrophages, monocytes and sensitized lymphocytes → [IL1, IL6, TNF] endogenous pyrogens → stimulation of the endothelial cells of the brain blood vessels → PG. E1& E2 → re-setting of the set point → fever

2- **Direct effect of some drugs**

- Like cocaine and phenothiazine and in some people dopamine antagonists

3- **Dopamine level**

- Affects directly the centre as occurs in neuroleptic malignant syndrome
- Neuroleptic malignant syndrome

- Occurs due to idiosyncrasy or overdose of certain drugs like haloperidol (sufenase) and phenothiazines (e.g. chlorpromazine)
- It causes lead pipe rigidity, dystonic movements and tremors of extrapyramidal origin followed by rise in body temp. that may lead to hypothermia
- Stupor or comma may occur

4- Other medications

- Can affect centrally the heat regulating centre like serotonin, A. choline and neuropeptides

5- CAMP and Na/Ca ion ratio may play a rule

- Malignant hyperthermia
  - Disorder of the skeletal muscles in congenitally susceptible persons, initiated by halogenated inhalation anesthesia or depolarizing agents like succenylcholine leading to generalized muscle contraction due to increased Ca influx
  - The sustained muscle rigidity leads to fever and hyperthermia

6- Disturbance of heat loss mechanism → as in heat illnesses

Hypothermia

Definition → central or core temperature ≤ 35 C (rectal temperature)

Causes

1- Myxedema coma

2- Hypoglycemia

3- Adrenal hypofunction

4- Hypopuitatrism

5- Alcohol (↑ heat loss by peripheral VD and inhibition of shivering)

6- Prolonged exposure to cold

Collections of tropical and infectious diseases

Parasites affecting different organs

Organ	Trematoda	Cestoda	Nematoda	Protozoa	Arthropods
Small intestine	*H heterophyes* *Fasciolopsis buski, Metagonimus yokogawai (not in Egypt)*	*D. latum* *T. solium* *T. saginata* *H. nana* *H. diminuta* *D. caninum*	*Ascaris* *Ancylostoma duodenale* *Trichostrongylus* *Strongyloides* *Trichinella* *Capillaria*	*Giardia lamblia* *Cryptosporidium* *Isospora* *Cyclospora* *Microsporidia* *Sarcocystis* Leishmania (in macrophage of the wall) P. falciparum (in B.V of the wall)	*Intestinal myiasis*
Large intestine	*Schistosoma mansoni* (in veins of the wall)	----------	*Enterobius* *Trichuris*	*Al amoebae except E. gingivalis* *Balantidium coli* Leishmania P. falciparum	*Intestinal myiasis*
Liver	*Fasciola* *Schistosoma* (adult, egg)	*Echinococcus granulosus (Hydatid cyst)* *Cysticercus cellulosae*	*Ascaris worm in the bile duct* Visceral larva migrans	*Entamoeba histolytica* *Giardia lamblia(in common bile duct)* *Visceral Leishmaniasis* *T. cruzi amastigot* *Plasmodium* *toxoplasma*	----------
Lungs	*Paragonimus* *Schistosoma*	*Echinococcus granulosus* (cyst)	*Ascaris* (larva) *Ancylostoma* (larva) *Strongyloides* (larva) Visceral larva migrans *M. perstans, M. ozzardi* (pleural sac) *W.bancrofti* (tropical pulmonary eosinophilia)	*Entamoeba histolytica* (abscess) *Pneumocystis carinii*	----------
Brain	Eggs act as emboli: - *Schistosoma japonicum* - *H heterophyes* *Paragonimus*	*Echinococcus granulosus* *Cysticercus cellulosae* Coenurus cyst Sparganosis	Visceral larva migrans *Strongyloides* (disseminated larva)	*Entamoeba histolytica (abscess)* *Neglaria and Acanthamoeba* *Trypanosoma* *P. falciparum* *Toxoplasma gondii*	----------

Organ	Trematoda	Cestoda	Nematoda	Protozoa	Arthropods
Eye	----------	Sparganum *Cysticercus cellulosae* Hydatid cyst (rare)	Visceral larva migrans *Trichinella* (larva in ex.o.m) *Loa loa* *Onchocerca*	*Acanthamoeba (Keratitis)* *T. cruzi (Romana's sign)* *Toxoplasma gondii* (retinochoroiditis)	Ocular myiasis *Phthirus pubis (in eye lashes)*
Heart	*Heterophyes*: eggs act as emboli	*Cysticercus cellulosae* *Echinococcus granulosus*	Visceral larva migrans *Trichinella (larva)* *M. perstans and M. ozzardi*	*T. cruzi* amastigotes *Toxoplasma gondii* *Sarcocystis*	----------
Lymph nodes [causes of lymphadenopathy]	----------	Sparganum	*Wuchereria bancrofti (LL, scrotum)* *Brugia malayi (UL, breast)* *O. volvulus*	*Trypanosoma* *Leishmania* *Toxoplasma gondii* (cervical, axillary)	----------
Skin & Subcutaneous tissue	*Schistosomes (egg granuloma)* *Bather's itch (cercariae of non-human schistosomes)*	Sparganum Cysticercus cellulosae	Cutaneous larva migrans *Dracunculus* *Loa loa* *Onchocerca*	*Leishmania* African Trypanosome (chancre) T. cruzi (Chagoma)	Cutaneous myiasis *Sarcoptes scabiei* *Tunga penetrans* *Demodex folliculorum* *House dust mites* *Storage mites*
Muscles	----------	Sparganum *Cysticercus cellulosae* Hydatid cyst (rare)	*Trichinella* VLM (rare)	*T. cruzi (leishmanoid form* *Toxoplasma gondii* *Sarcocystis lindemanii*	----------
Blood [i.e. appear in blood film]	---------- لاحظ ان ديدان البلهارسيا تعيش داخل الوعاء الدموى لكن لا تظهر فى blood film	----------	*Wuchereria bancrofti* *Brugia malayi* *Loa loa* (microfilaria) *M. perstans and M. ozzardi*	*Trypanosoma (outside RBCs)* *Leishmania (inside macrophages)* Plasmodium (inside RBCs) *Babesia* (inside RBCs) T. gondii (*inside macrophages*)	----------
Urine	*Schistosoma haematobium* egg *(may be mansoni 5%)*	Hydatid sand from ruptured kidney cyst	*Enterobius eggs* (in females) *Wuchereria bancrofti* microfilaria (chyluria)	*Trichomonas vaginalis* *L. donovani* *P. falciparum (black water fever)*	Urogenital myiasis *phthirus pubis* *Sarcoptes*

Sputum	Eggs of: □ *Paragonimus* □*S.haematobium*	□ Hydatid sand from ruptured lung cyst	□ *Ascaris* (larva) □ *Ancylostoma* (larva) □ *Strongyloides* (larva**)**	□ *E. histolytica trophozoite* (from amoebic lung abscess eroding a bronchus) □ *E. gingivalis trophozoite*	----------
Semen	□ S. haematobium ova (haemospermia)			□ *T. vaginalis*	□ *Phthirus pubis*
RES	----------	----------	----------	□ *Leishmania* □ *T. cruzi* □ *P. falciparum* □ *Toxoplasma*	----------

Clinical presentations caused by parasites

Disease	Trematoda	Cestoda	Nematoda	Protozoa	Arthropods
Diarrhea	*Heterophyes* *Fasciolopsis buski, Metagonimus yokogawai (not in Egypt)*	All adult Cestoda لا تنسى الدودة نانا	Hook worms *Ascaris* *Strongyloides (bloody)* *Trichinella* *Capillaria*	Giardia lamblia (fatty) Cryptosporium Cyclospora Isospora Intestinal microsporidia Visceral Leishmania Malignant malaria (P. falciparum)	----------
Dysentery	*Schistosoma mansoni*	----------	*Trichuris*	*Entamoeba histolytica* *Balantidium coli* P. falciparum Visceral Leishmania	----------
Fever	*Fasciola* *Schistosoma* (Katayama s)	*Echinococcus granulosus (if ruptured into the blood)*	VLM *Trichinella* Filaria (bancrofti & malayi	Amoebae Potentially pathogenic amoeba Trypanosoma Visceral Leishmania Plasmodium Babesia Toxoplasma	----------
Jaundice	*Fasciola* *Schistosoma Mansoni (10-20% haematobium)*	*Echinococcus granulosus* (cyst)	Ascaris Visceral larva migrans (VLM)	Amoebae (abscess) P. falciparum Toxoplasma	----------
Hepatomegaly	*Fasciola* *Schistosoma*	*Echinococcus granulosus*	VLM	Amoebae Visceral Leishmania Trypanosome Plasmodium Toxoplasma	----------
Splenomegaly	*Schistosoma*	----------	----------	Visceral Leishmania Trypanosoma Plasmodium	----------
Itching (pruritus)	Cercarial dermatitis	---------- ↓	Hook worms CLM *Onchocerca* *Loa loa* ↓	----------	Sarcoptes scabiei Insect bites House dust mites Pediculosis
Pruritis ani	----------	*Taenia saginata* ↑	*Enterobius* ↑	----------	----------

Haematuria		□ *Schistosoma haematobium*	----------	----------	□ Plasmodium	----------
Rectal prolapsed		----------	----------	□ *Trichuris*	□ *Trichuris*	----------
Appendicitis		----------	□ *T. saginata* □ *E. vermicularis*	□ *Ascaris* □ *Trichuris*	□ E. histolytica □ B. coli	----------
Ulcer		----------	----------	□ *Trichuris* □ *Ancylostoma* □ *D. medinensis*	□ E. histolytica □ B. coli □ Cutaneous Leishmania □Acanthamoeba □ Microsporidia	□Siphonaptera (Fleas) □ Acarina (Ticks) □ Myiasis
Anemia	Microcytic hypochromic	□ *Schistosoma*	----------	□ *Trichuris* □ Hookworms	----------	----------
	Macrocytic hyperchromic	----------	□ *D. latum* (vit. B12 deficiency)	□ *Trichuris* (due to toxic products	----------	----------
	Normocytic	□ *Schistosoma*	----------	----------	□ Plasmodium □ Babesia	----------
	Hypoplastic	----------	----------	----------	□ Leishmania □ Trypanosoma	----------
Cystic mass in the liver		□ *Fasciola liver abscesses*	□ *Hydatid cyst*	----------	□*Amoebic liver abscess*	----------
Coma		----------	----------	----------	□ Cerebral malaria □ African trypanosome □ 1ry amoebic meningoenceph. (Naegleria and Acanthamoeba) □ Cerebral toxoplasmosis	- ----------
Bronchial asthma		□Schistosoma □Paragonimus		□occult filariasis □VLM □Larvae of Ascaris, Ancylostoma and Strongyloides □Capillaria aerophila	□Pneumocystis carinii	□Mites or decay products of dead mites [except sarcoptes, Demodex and Trombicula]
Endemic hemoptysis		□ Paragonimus	□*Echinococcus granulosus*			

Modes of transmission of parasites

Mode		Trematoda	Cestoda	Nematoda	Protozoa	Arthropods
Vegetables		*Fasciola* *Fasciolopsis buski*	*Taenia solium egg* *H. nana* *Echinococcus* *M. multiceps*	*Ascaris* *Enterobius* *Trichuris* *Toxocara (VLM)* *Trichostrongylus* and Trichocephalus	*Amoebae* *Giardia lamblia* *B. coli* *Toxoplasma gondii* *Cryptosporidium* *Isospora* *Cyclospora*	Eggs of flies as Musca causing gastric or intestinal myiasis.
Water [all mentioned above with vegetables]		*Fasciola* *Schistosoma* **cercariae penetrate the skin in contact with water**	*Sparganum (inside Cyclops)* *Taenia solium eggs* *H. nana* *Echinococcus* *M.multiceps*	*Ascaris* *Enterobius* *Trichuris* *Toxocara (VLM)* *Trichostrongylus* *D. medinensis* (*inside Cyclops*)	Potentially pathogenic free-living amoebae through contact with water	----------
Undercooked fish		*Heterophyes* *Paragonimus*	*D. latum*	*Capillaria*	----------	----------
Undercooked viscera/ meat		*Halzoun* - Fasciola - Linguatula nymphs	Sparganum *Taenia* -Saginata (beef), Solium (pork)	Trichinella spiralis (Pork)	*Toxoplasma gondii*	----------
Auto-infection		----------	*H. nana* *Taenia solium* eggs **[internal]**	*Enterobius* ***[internal, ext]*** *Strongyloides* ***[internal, ext]*** *Capillaria* **[internal]**	*Entamoeba histolytica* *Balantidium coli* *Giardia lamblia* *Cryptosporidium* *Isospora*	----------
Inhalation		----------	----------	*Enterobius*	Potentially pathogenic free-living amoebae pneumocystis carinii	----------
Congenital or by **blood transfusion**		----------	----------	----------	*Toxoplasma gondii* Plasmodium *T. cruzi* *Visceral leishmaniasis*	----------
Arthropodes	**Biological**	----------	*D. latum* Sparganum *H. nana* *H. diminuta* *D. caninum*	*D. medinensis* All filaria	*Leishmania* *Trypanosoma* *Plasmodium* *Babesia*	----------
	Mechanical	Eggs (Musca)	----------	----------	Cysts (musca)	Blood parasites on mouth parts of bitting flies
Sexual		----------	----------	----------	T. vaginalis Giardia, E. histolytica (autoinfection)	Scabies Pediculosis Phthirus pubis

Causes of eosinophilia

1- The upper limit of normal for eosinophils is usually taken to be 0.4x10^9/l.

2- In general protazoal infections do not produce eosinophilia. Helminths do cause eosinophilia and the degree of eosinophilia is related to the extent of tissue invasion by the helminth.

3- Filarial worms often cause a high eosinophilia whereas the intestinal nematodes tend to cause only a modest increase in the eosinophil count

Important parasitic causes of eosinophilia

Trematoda	Fascioliasis Schistosomiasis Paragonimus
Cestoda	Tissue cestodes - Hydatid disease - Coenurus cyst - Sparganum - Cysticercus cellulosae
Nematode	Tissue nematode - All filarial worms - Tropical pulmonary eosinophilia - VLM - Trichinella spiralis - Dracunculus Loffler's syndrome [Ascaris, Ancylostoma, Strongyloides] and other intestinal nematodes Capillaria hepatica
Protozoa	Toxoplasmosis Cryptosporidium Pneumocystis carinii (may be present)

Non-parasitic causes of eosinophilia

Allergic disorders	Allergic disorders Asthma Eczema Hayfever Drug hypersensitivity
Auto-immune	Churg-Strauss syndrome Wegener's granulomatosis Polyarteritis nodosa
Haematological	Hodgkin's disease Eosinophilic leukaemia
Dermatological	Bullous pemphigoid Pemphigus vulgaris
Respiratory	Allergic bronchopulmonary aspergillosis Hypereosinophilic syndrome Asthma
Miscellaneous	Eosinophilia-myalgia syndrome caused by L-Tryptophan Spanish toxic oil syndrome Eosinophilic gastroenteritis

Ocular manifestations in the tropics

1- Conjunctivitis

2- Keratitis

3- Uveitis

4- Retinitis

5- Optic neuritis

6- Lesions of the adnexa including:

- Ulcerative lesions of the eyelid
- Parinaud's oculoglandular syndrome (an ulceronodular conjunctival/corneal lesion with associated preauricular adenopathy)
- Proptosis
- Conjunctival, intraocular, or orbital “worm.”

7- Significant visual loss and blindness esp. with

- Trachoma
- Onchocerciasis
- Measles/xerophthalmia
- Leprosy

Manifestations of parasites in the eye

Parasite	Main manifestations
Sparganum	Painful oedematous conjunctivitis and ptosis
Cysticercus cellulosae	Visual disturbances
Visceral larva migrans	Visual disturbances or sudden blindness in the affected eye & may present as strabismus (squint)
Trichinella spiralis larvae	Edema of eyelids and difficulty of eye movements
Loa loa	Adult worm may seen in the conjunctiva or eyelids (intense pain, inflammation, irritation and lacrimation) Retinal hemorrhage, recurrent chorioretinitis but does not cause blindness
Onchocerca volvulus	1st symptoms → photophobia, lacrimation, blepherospasm and foreign body sensation Keratitis, iridocyclitis, chorioditis, retinitis and optic neuritis Complete blindness
Acanthamoeba	Ulcerative keratitis (severe ocular pain and affection of vision)
Trypanosoma cruzi	(Romana's sign) → sudden unilateral edema of the upper and lower eyelids and cheek usually with conjunctivitis
Toxoplasma gondii	Retinochoroiditis which can result in blindness
Ocular myiasis	External ophthalmomyiasis → conjunctival irritation and severe pain Internal → loss of the eye
Phthirus pubis (in the eye lashes)	Blepharitis

Fever presenting with <u>coma</u> and/or <u>convulsions</u>

Infections	Meningitis * Encephalitis Meningo-encephalitis Viral hemorrhagic fever Cerebral malaria * Trypanosomiasis Typhoid state Typhus
Neurological causes	Pontine haemorrhage * Subarachnoid haemorrhage * Brain abscess Brain tumors Status epilepticus Febrile seizures (9 mo- 6 yr)
Physical causes	Heat or sun stroke * Dehydration Atropine poisoning Amphetamine dependence? Adrenergic bronchodilator overdose
Endocrinal causes	Thyrotoxic crisis Addisonian crisis?
Any commatosed patient with superadded infection	e.g. DKA or hepatic coma

Causes of fever with jaundice

Viral causes	□ Acute viral hepatitis HAV, HBV, HCV, HDV, HEV (the commonest cause) EBV, CMV, HSV and yellow fever virus □ Infectious mononucleosis □ Congenital rubella syndrome □ HIV □ Viral hemorrhagic fevers □ Rift valley fever
Bacterial causes	Paratyphoid B **fever** Q **fever** Relapsing **fever** Charcot's **fever** [ascending cholangitis] **S**epticaemia **S**yphilis of the liver Leptospirosis, Weil's disease Chlamydial infection Legionella. Pyogenic liver abscess 2ry infection of gallstones
Parasitic causes	Falciparum malaria [black water fever] Hydatid liver cyst [16%] Amoebic liver abscess [10%] Fascioliasis Hepatic flukes
Neoplastic	Liver neoplasms (primary or secondary). Cancer head of pancreas
Hematological causes	Acquired or congenital hemolytic anemia e.g. Haemolytic crisis Acute leukemia
Others	Alcoholic liver disease Acute pancreatitis Common bile duct stone Drug induced hepatitis Cirrhosis

Causes of nephrotic syndrome in the tropics

Viral	Hepatitis B
Bacterial	*Beta-heamolytic streptococci * Leprosy
Parasitic	*Plasmodium malariae *Schistosoma mansoni Filarial worms
Others	*Lupus nephritis Minimal change glomerulonephritis Renal vein thrombosis Amyloidosis Diabetes Multiple myeloma

Uses of steroides in tropical diseases

Steroids beneficial	Steroids of no benefit
1. Severe typhoid. 2. Hib meningitis in children. 3. Croup. 4. Severe pneumocystis pneumonia. 5. Type 1 lepra reaction. 6. Tuberculoid leprosy. 7. Tuberculous meningitis, pericarditis, pleural effusion. 8. Katayama fever.	1. Meningococcal disease 2. Gram negative septicemia. 3. Herpes Zoster. 4. Cerebral malaria. 5. Visceral Leishmaniasis.

Tumors associated with infective agents

Tumour	Associated infective agent
Burkitt's lymphoma	EBV
Nasopharyngeal carcinoma	EBV
Hodgkin's disease	EBV
Squamous carcinoma of penis	Human papilloma virus
Carcinoma of cervix (and vulva)	Human papilloma virus
HCC	Hepatitis B (also hepatitis C)
Adult T cell leukemia/lymphoma	HTLV 1 & 2
Hairy cell leukemia	HTLV
Kaposi's sarcoma	Human herpes virus 8, HIV
Cholangiocarcinoma	Clonorchis sinensis
Squamous carcinoma of urinary bladder	Schistosoma haematobium
Cancer colon	Schistosoma japonicum (mansoni ??)
Basal cell carcinoma of the skin	Leishmania tropica (oriental sore)
Cancer rectum	Chronic amoebiasis

N.B. Parasites with malignant like behaviour are: alveolar hydatid of E. multilocularis & cysticercus racemosus

Infectious causes of dementia

Infectious agent	Illness
Measles or rubella	Subacute sclerosing panencephalitis (SSPE)
HIV	AIDS dementia
Treponema pallidum	General paresis of the insane (tertiary syphilis)
Borrelia burgdorferi	Lyme disease
Prions	Creutzfeld-Jakob disease

Causes of massive splenomegaly

Causes of huge splenomegaly	
Parasitic causes	Chronic visceral leishmaniasis* **Malaria or hyper-reactive malaria splenomegaly** Portal HTN e.g. caused by schistosomiasis, cirrhosis Splenic hydatid cyst
Hematological causes	Rapidly progressive Lymphoma, Chronic myeloid leukemia, hairy cell leukemia and myelodysplasia Haemoglobinopathies and hereditary haemolytic anaemias
Others	Splenic vein thrombosis Still's disease Glycogen storage disease, adult Gaucher's disease and other metabolic diseases Amyloidosis

Causes of just palpable to moderate spleen

Causes of just palpable to moderate splenomegaly	
A	Any of the above (initial stage)*
B	Bacterial endocarditis * Brucellosis
C	CMV*
E	Echinococcosis
I	Infectious mononucleosis *
H	HIV
L	Leptospirosis Lyme disease
R	Relapsing fever Rickettsiosis
S	Syphilis (2ry) Sarcoidosis * SLE *
T	Typhoid and paratyphoid * Typhus Tuberculosis (miliary)
	Toxoplasmosis Trypanosomiasis - Polycythaemia rubra vera*

Reasons for enlarged spleens

1- In response to a need for **excess physiological activity** e.g.

- Phagocytosis of abnormal RBCs as in haemoglobinopathies
- Antibody production to combat infection

2- Because of a **structural abnormality** e.g.

- Portal HTN
- Infiltration by malignant cells

Diseases transmitted from mother to foetus or newborn

Prenatal transmission (Transplacental)	
Syphilis	Congenital syphilis
Listeria monocytogenes	Abortion or still birth
Rubella	Congenital rubella syndrome
Cytomegalovirus	Cytomegalic inclusion disease
Varicella	Congenital varicella syndrome
HIV	AIDS
Parvovirus B19	Hydrops foetalis
Toxoplasma	Toxoplasmosis
Perinatal transmission	
Herpes simplex	Herpes neonatorum
HIV	AIDS
HTLV	T cell lymphoma
Hepatitis B	Hepatitis B carrier state
Cytomegalovirus	Subclinical infection
Coxsackie B virus	Neonatal myocarditis
Gonococci	Neonatal ophthalmia
Chlamydia	Inclusion conjunctivitis, pneumonia
Strept. agalactiae	Neonatal meningitis
Listeria monocytogenes rarely	Neonatal meningitis

Modes of transmission

1- The organisms can be transmitted **transplacentally** (prenatal)

2- Or they are contracted from the birth canal during labour (**perinatal**) due to contamination of the baby by maternal blood, vaginal discharge and stools or other forms of contact e.g. breast milk or saliva shortly after birth

Diagnosis

1- **Detection of IgM antibodies** to the different viruses

2- **Serological tests** for syphilis

3- **The TORCH test** for diagnosis of neonatal infections

- **T**oxoplasma
- **R**ubella
- **C**MV
- **H**erpes simplex virus
- **H**IV

  [detection of IgM antibodies in the sera of the newborn]
- **O** stands for others which include varicella and syphilis

Organisms transmitted by blood transfusion

Organism	Comment
HIV 1 and 2	-------
Hepatitis viruses B,C,D	-------
CMV, EBV, HTLV	Transmitted in blood cells but not in plasma
Parvovirus B 19	Rare
Treponema pallidum, malaria	Transmitted in fresh blood as they die when refrigerated after few days
Donated blood should be tested for 1- HBsAg, HBcIgM 2- HCV 3- HIV1 and 2 4- HTLV1 and 2 5- Test for syphilis (VDRL) 6- Serum transaminases assay (indicate liver affection)	

Infections causing bacteremia or toxemia

Bacteremia	Toxemia
1- Enteric fever 2- Brucellosis 3- Meningitis 4- Endocarditis 5- Puerperal sepsis 6- Relapsing fever 7- Epidemic and endemic typhus	1- C.diphtheria 2- Cl.tetani 3- Cl.botulinum 4- Cl. Perfringens 5- Cl. Difficile 6- S. aureus TSS 7- Strept. Pyogenes pyrogenic toxin

Organisms causing urinary tract infection

Bacterial	- E. coli (60-90%) - klebsiella, proteus and pseudomonas - S. aureus, S. epidermidis and S. saprophyticus - Enterococcus faecalis, Bacteroides fragilis - N. gonorrhoeae - M. tuberculosis
Fungal	Candida albicans
Viral	Adenoviruses
Sterile pyuria [pus without growth on ordinary media]	- Renal tuberculosis - Prior antibiotics - Anaerobes - Mycoplasma, Ureaplasma, Chlamydia - Viruses

Common nosocomial infections

Urinary tract infections	- E. coli is the commonest cause - klebsiella, pseudomonas and proteus
Surgical wound infections	- S. aureus, gram -ve bacilli and anaerobes
Lower respiratory tract infections especially pneumonia	- S. aureus and gram negative bacilli
Bacteremia or septicemia	- Bacteroids, S. aureus, serratia,…
Gastrointestinal infections	- Pseudomembranous colitis by Cl. difficile

Causative organisms of pneumonia

Bacterial	- Strept. Pneumonia, kl. Pneumoniae - S. aureus, strept. Pyogenes, H. influenzae - Pseudomonas aeruginosa, proteus - Y. pestis, M. tuberculosis and anaerobic organisms
Viral	- Influenza and parainfluenza viruses, RSV, measles, adenoviruses, varicella zoster and SARS
Fungal	- Pneumocystis jiroveci, Cryptococcus neoformans, histoplasma and coccidioides
Atypical pneumonia	- Mycoplasma pneumoniae, Chlamydia pneumoniae, Chlamydia psittaci, legionella pneumophila, coxiella burnetii - viral and fungal pneumonias

Main sexually transmitted diseases

Disease	Causative agent
Gonorrhea	N. gonorrhoeae
Syphilis	T . pallidum
Chancroid or soft sore	H . ducreyi
Lymphogranuloma venereum	C .trachomatis types L1-L3
Non-specific urethritis	C . trachomatis types D-K
Genital herpes	Herpes simplex type 2
Genital wart	Papilloma virus
Hepatitis B and C less commonly	
AIDS	HIV
T cell lymphoma	HTLV

Urethritis

1- Specific gonococcal urethritis
2- Non specific urethritis
   - Chlamydia trachomatis (main cause)
   - Mycoplasma and ureaplasma urealyticum
   - Candida albicans
   - Trichomonas vaginalis
3- Staphylococci, E. coli, streptococci → cause post traumatic infections after catheterization or instrumation
4- Adenoviruses, herpes simplex virus and human papilloma virus

Diagnosis

1- Urethral discharge is examined directly by
   - Wet smear → for trichomonas
   - Gram stained smear → will show pus cells and the organisms
   - Immunofluorescence or ELISA → for Chlamydia
2- Discharge is cultured for the different organisms

Milk borne diseases

From the infected animals and excreted in milk
1- Bovine tuberculosis 2- Brucellosis 3- Q fever 4- Toxoplasmosis (infected goat milk) 5- Listeria monocytogenes rarely
From milk contaminated by milk handlers or other sources
1- Salmonella infections 2- Shigellosis 3- Staphylococcal food poisoning 4- Campylobacter 5- Cholera 6- Hepatitis A and E 7- Poliomyelitis 8- Rotavirus

Bioterrorism agents

1- Small pox
2- Anthrax
3- Botulism toxin
4- Plague
5- Viral haemorrhagic fevers
6- Tularemia

The value of direct smear in diagnosis

1- <u>Detection of organisms</u> in direct smear **<u>may be sufficient for diagnosis</u>** in:

- <u>Leprosy</u> → nasal scrapings by modified Z.N stain
- <u>Vincent angina</u> → smears from lesions show pus cells, spirochaetes and fusiform bacilli
- <u>Syphilis</u> → smears from chancre show spirochaetes
- <u>Relapsing fever</u> during the fever → borrelia in blood film
- <u>Acute male gonorrhea</u> → gram negative diplococcic in pus cells
- <u>A case of cholera during an epidemic</u> → motile curved rods in stools

2- **The information given by direct smears** may be **urgently needed to start treatment** before culture results appear as in:

- Meningitis → CSF deposit may show the causative organism
- Tuberculosis → acid fast bacilli in sputum by Z.N. stain
- Diphtheria like organisms → are reported to help clinicians start treatment

3- **The presence and concentration of organisms** in smears may give an **indication of the organism involved**:

- Presence of pneumococci in large numbers in sputum smears are suggestive of pneumococcal pneumonia
- Appearance of organisms in smears and no growth in aerobic cultures may point to anaerobes

Acute abdominal pain in tropics

1- Abdominal tuberculosis

2- Typhoid fever including perforation

3- Amoebic colitis including perforation

4- Hydatid cyst rupture

5- Amoebic liver abscess (which may rupture)

6- I.O. caused by **ascaris** lumbricoides

7- Ectopic **ascariasis** e.g. biliary and/or pancreatic obstruction

8- Hyperinfection syndrome pf **strongyloides**

9- Sickle cell crisis

10- Splenic rupture

11- Non tropical causes

- Appendicitis
- Biliary colic and cholecystitis
- Mesenteric adenitis
- Perforated peptic ulcers
- Intestinal obstruction

Fever with epistaxis

1- Acute typhoid fever
2- Acute rheumatic fever
3- Infective endocarditis
4- Acute leukemia
5- Lymphoma
6- Vasculitis
7- Hemorrhagic forms of exanthemata
    - Spirochetal diseases (leptospirosis, Lyme disease and relapsing fever)
    - Viral hemorrhagic fever

Fever with pallor

1- Infective endocarditis

2- Acute rheumatic fever

3- Hemolytic crisis

4- Malaria

5- Malignancies e.g. acute leukemia

Fever with herpes labialis

1- Common cold and influenza

2- Malaria

3- Meningococcal meningitis

4- Pneumonia

Fever with headache

1- Meningitis and encephalitis → headache usually occipital and severe

2- Influenza and common cold

3- Typhoid fever → headache usually frontal dull aching

4- Rift valley fever and dengue

5- Malaria

Fever presenting by pains

1- **Eye pains** → mostly viral in origin
2- **Backache**
   - Influenza
   - Meningitis, encephalitis and meningoencephalitis
   - Rift valley fever
   - Brucellosis
3- **Chest pain**
   - Influenza
   - Broncho or lobar pneumonia
   - Pleurisy (FMF)
4- **Abdominal pain**
   - Typhoid perforation and peritonitis
   - TB peritonitis
   - Amoebic hepatitis
   - Rift valley fever
   - Referred from lobar pneumonia esp. in children

Precautions taken by travelers to tropical areas

Active immunization

1- **Viral**
   - Poliomyelitis
   - Rabies
   - Yellow fever
   - Japanese encephalitis
   - Hepatitis B
2- **Bacterial**
   - Typhoid
   - Cholera
   - Meningoencephalitis
   - TB (BCG)

Passive immunization

1- Hepatitis A Ig
2- Hepatitis B Ig

Chemoprophylaxis

1- Malaria
2- Traveller's diarrhea

Emergencies in fevers

Acute toxemia	- Diphthera, tetanus, meningitis, cholera, enterica, puerperal sepsis
Acute intestinal hemorrhage	- Acute enteric fever, rift valley fever
Dehydration	- Cholera, bacillary dysentery, other causes of GE
Ascending paralysis	-poliomyelitis, Guillain Barre syndrome
Descending paralysis	- Diphtheria, meningitis, encephalitis, tetanus, rabies, botulism
Acute abdomen	-Typhoid perforation, pancreatitis complicating mumps, rupture amoebic liver abscess
Coma	-Meningitis, encephalitis, meningoencephalitis, cerebral malaria, heat stroke, cerebral and pontine hemorrhage, hepatic coma, DKA with infection, atropine poisoning
Urgent dyspnea	- Mechanical obstruction from spasm, edema or exudation → diphtheria (membrane), tetanus (spasm), serum allergy (edema), fungal laryngotracheobronchitis (no membrane or foreign body) and rupture of amoebic liver abscess into the pericardium. Dyspnea and stridor are presenting symptoms
	- Paralysis of respiratory muscles → diphtheritic neuritis, rabies, Guillain Barre syndrome. There is dyspnea with no stridor

Fever with rigors or chills

1- Acute pyelonephritis (UTI)
2- Malaria
3- Amoebic hepatitios
4- Infective endocarditis
5- Charcot's fever (ascending cholangitis)
6- Abscess elsewhere (subphrenic, perinephric, liver abscess, puerperal sepsis)
7- Septicemia and pyaemia
8- Hemolytic crisis
9- Brucellosis
10- Rickettsial diseases

1- **Any fever with sudden onset** is accompanied with rigors in the beginning as in lobar pneumonia, influenza, tonsillitis
2- **Chills** → sensation of cold occurring in most fevers
3- **Rigors** → chills + shivering with teeth chattering
4- **Sweats** occur with activation of heat loss mechanisms either due to use of antipyretics or to elimination of the febrile stimulus

Fever with relative bradycardia

Fever without CNS involvement	Lesions of the CNS with rapid ↑ in the ICT
1- Influenza 2- Typhoid fever 3- Infective hepatitis 4- Mumps 5- 1ry atypical pneumonia	1- Cerebro-spinal fever 2- TB meningitis 3- Brain abscess 4- Pontine hemorrhage

Causes of sore throat

1- **Viral pharyngitis** (adenovirus)

2- **Acute follicular tonsillitis** (streptococci)

3- **Infectious mononucleosis**

4- **Herpangina** (coxsackie virus)

5- Diphtheria

6- Ludwig's angina (microaerophilic streptococci)

7- Vincent's angina (borrelia vincenti + bacillus fusiformis)

8- Epiglottitis (H. influenza)

9- Candidiasis

10- **Acute lymphoblastic leukemia**

11- **Agranulocytosis**

12- **Aplastic anemia**

13- Glossopharyngeal neuralgia

Opportunistic infections (mostly in immuno-compromised host)

1- Cryptosporidium

2- Isospora

3- Cyclospora

4- Toxoplasma

5- Potentially pathogenic free-living amoeba

6- Microspoidia

7- Pneumocystis carinii

8- Strongyloides

Zoonotic diseases

Definition

1- These are diseases that are primarily affect **vertebrate animals** (other than man) but which under certain circumstances are **transmissible to man**

2- **Man acquires infection** from the animal reservoir by

- Direct contact
- Ingestion of infectious tissue or milk
- Vectors e.g. fleas, ticks or mosquitoes

Bacterial zoonoses	1- Brucellosis 2- Bovine & avian TB 3- Salmonellosis (S. enteritidis) & S. typhi murium 4- Anthrax 5- Plaque 6- Tetanus 7- Tularemia 8- Melioidosis & glanders 9- Listeriosis 10-Cat scratch disease 11-Erysipeloid 12-Dog bite fever 13-**Y**.enterocolitica 14- **P**asteurella multocida (cellulitis) 15- **C**ampylobacter jejuni, Chlamydia psittaci 16-**E**.coli O157:H7
Spirocheatal zoonoses	1- Leptospirosis 2- Tick born relapsing fever 3- Lyme disease
Rickettsial zoonoses	1- Q fever 2- Rocky mountain spotted fever 3- Murine typhus 4- Scrub typhus
Viral zoonoses	1- Rabies 2- Yellow fever 3- Dengue fever 4- Lassa fever 5- Rift valley fever 6- Hantavirus 7- Group B arbovirus encephalitis (tick borne encephalitis group, mosquito borne infection: dengue, Japanese B encephalitis, West Nile, yellow fever 8- Orf 9- New castle disease (myxovirus)

Parasitic zoonoses	1- Hydatid disease 2- T.saginata and solium 3- H. nana and diminuta 4- Fasciola hepatica 5- Clonorchis sinensis 6- Fasciolopsis buski 7- H.heterophes 8- Trichinella spiralis 9- Toxocariasis 10-D. latum 11-Ganthostomiasis 12-Angiostrongylus cantonesis 13-Onchocerciasis 14-Toxoplasmosis 15-Leishmania donovani 16-Chaga's disease 17-Cryptosporidiosis 18-Babesiosis 19-Balantidiasis 20-Screw worm myiasis
Fungal zoonoses	1- Actinomycosis 2- Coccidioidomycosis 3- North American blastomycosis 4- Histoplasmosis 5- Trichophytosis

Causes of diarrhea in HIV patients

1- **Bacterial Small-bowel Pathogens**

- Salmonella (treated by cotrimoxazole or, ciprofloxacin).
- Mycobacteria avium complex (treated by azithromycin, clarithromycin or ciprofloxacin)

2- Protozoa Small Bowel Pathogens

- Cryptosporidium (treated by azithromycin, paromomycin).
- Microsporidia (treated by azithromycin, paromomycin).
- Isospora belli (treated by cotrimoxazole).
- Cyclospora (treated by cotrimoxazole).

3- Bacterial Large-bowel Pathogens (treated by ciprofloxacin)

- Shigella.
- Campylobacter
- Clostridium difficile (treated by metronidazole or vancomycin).
- Vibrio parahaemolyticus acute colitis treated by (doxycycline of ciprofloxacin).
- Enterohemorrhagic or Verocytotoxin-Producing E. coli (hemorrhagic colitis).

4- Viral Large Bowel Pathogens

- Cytomegalovirus (treated by IV gancyclovir or oral valgancyclovir for 3 weeks).

5- HIV Small Bowel Enteropathy HIV itself may cause a chronic diarrhea in AIDS patients.

Infectious causes of fever in HIV patient

Meningitis/encephalitis/other CNS disorders	Any CD4+ → streptococcus pneumoniae, neisseria meningitidis, listeria monocytogenes, HSV
	CD4+ < 100 → Cryptococcus neoformans, toxoplasma gondii (encephalitis, cerebral abscess)
	CD4+ < 50 → CMV and VZV (encephalitis), EBV associated lymphoma, JC polyomavirus (progressive multifocal leukoencephalopathy)
Pneumonia	Any CD4+ → S.pneumoniae, H.influenzae, mycoplasma pneumoniae, legionella pneumophila, S.aureus, mycobacterium tuberculosis
	CD4+ < 200 → pneumocystis jiroveci, endemic fungi
	CD4+ < 100 → C.neoformans, T. gondii
	CD4+ < 50 → mycobacterium avium amplex, aspergillus spp., CMV, VZV
Esophagitis	CD4+ < 200 → candida albicans, CMV, HSV
Diarrhea	Any CD4+ → salmonella, shigella, campylobacter, E.coli, L. monocytogenes, Cl. Difficile, rotavirus, norovirus, giardia lamblia
	CD4+ < 100 → CMV (colitis), cryptosporidium, microsporidia, cyclospora, isospora
Rash	Any CD4+ → staphylococcus and streptococcus spp. (cellulitis, abscess), VZV (herpes zoster)
Disseminated infection	CD4+ < 100 (geberally) → mycobacterium avium complex, mycobacterium tuberculosis, histoplasma capsulatum, coccidiodes immitis, bartonella henselae, penicillium marneffei, Cryptococcus neoformans
N.B. there are several important opportunistic infections not typically associated with fever are included as well	

Protozoa causing diarrhea

1- Entameba histolytica

2- Giardia spp

3- Balantidium coli

4- Cryptosporidium spp

5- Microsporidia.

6- Cyclospora.

7- Isospora belli.

Infections causing fever + lymphadenopathy

Distribution	Potential causes	
Generalized	1- Cat scratch disease 2- Brucellosis 3- Typhoid fever 4- 2ry syphilis 5- Mycobacteria 6- Leptospirosis 7- Histoplasmosis 8- Coccidioidomycosis 9- Blastomycosis	10- CMV 11- EBV 12- HIV 13- Rubella 14- Rubeola 15- Dengue 16- Toxoplasmosis 17- Visceral leishmaniasis
Cervical	1- Streptococci (group A) 2- Mycobacteria 3- Diphtheria	4- EBV 5- Numerous other viruses
Inguinal	1- Syphilis (1ry) 2- Chancroid 3- HSV	4- Lymphogranuloma venereum 5- Granuloma inguinale
Regional	1- Streptococci 2- Staphylococci 3- Syphilis (2ry, epitrochlear) 4- Sporotrichosis 5- Tularemia 6- Typhus 7- Toxoplasmosis 8- Trypanosomiasis	9- Cat scratch disease 10- Mycobacteria 11- Filariasis 12- Plaque 13- HSV

Causes of suppurative lymphadenopathy

1- Strep. Pyogenes
2- Tuberculosis
3- Plague
4- Chancroid
5- Cat scratch fever
6- Tularaemia
7- Lymphogranuloma venereum

N.B. Sarcoidosis, HIV and syphilis do not generally cause suppurative lymphadenopathy.

N.B. Fever + mediastinal LN → sarcoidosis, TB, lymphoma and leukemia

Fever with lymphadenopathy

Viral causes	Infectious mononucleosis CMV HIV Measles & german measles Acute infectious lymphocytosis
Bacterial causes	Follicular tonsillitis and dental sepsis Scarlet fever Vincent's angina Diphtheria Brucellosis TB Anthrax Plague Cat scratch disease Tularaemia Leptospirosis Lyme disease Lymphogranuloma venereum Syphilis (2ry) Suppurated inguinal LN with Chancroid
Parasitic causes	Leishmaniasis Toxoplasmosis Trypanosomiasis Pediculosis and scalp infections ↑
Hematological causes	Acute lymphoblastic leukemia Chronic lymphoblastic leukemia Hodgkin's lymphoma Lymphosarcoma
Drugs	Antiepileptics e.g. hydantoins (small LN enlarg.)
Others	Still's disease Felty's disease Sarcoidosis

Infectious causes of fever with rash

Rash	Potential causes	
Petechiae/purpura (hemorrhagic rash)	1- Meningococcemia 2- Gonococcemia 3- Subacute bacterial endocarditis 4- Relapsing fever 5- Rocky mountain spotted fever 6- Rat bite fever	7- Viral hemorrhagic fevers 8- Enterovirus 9- EBV 10- Rubella 11- Hepatitis B (acute)
Macules/papules	1- Meningococcemia 2- Gonococcemia 3- Mycoplasma 4- Lyme disease 5- Typhoid fever (rose spots) 6- Typhus (epidemic, murine and scrub) 7- RMSF and other rickettsia 8- Syphilis (2ry)	9- Enterovirus 10- Adenovirus 11- EBV 12- Rubella 13- Hepatitis B 14- HHV-6 15- HIV 16- Parvovirus B19 17- Rubeola 18- Coxsackievirus 19- Dengue
Nodules	1- Ecthyma gangrenosum (pseudomonas sepsis) 2- Disseminated atypical mycobacterial infection	3- Disseminated fungal infection (candidiasis, histoplasmosis, blastomycosis, coccidioidomycosis, sporotrichosis)
Erythema nodosum	1- Streptococcus spp. 2- Yersinia spp. 3- Mycoplasma pneumonia 4- Chlamydia spp.	5- Mycobacteria 6- Histoplasmosis 7- Coccidioidomycosis
Vesicles	1- Enterovirus 2- Echovirus 3- HSV	4- VZV 5- Coxsackievirus (hand-foot-mouth) 6- Poxviruses
Pustules	1- Pseudomonas aeruginosa 2- Staphylococcus spp.	3- Gonococcemia
Bullae	1- Streptococcus spp. (A) 2- Staphylococcus spp.	3- Pseudomonas aeruginosa 4- Vibrio vulnificus
Ulcers	1- Anthrax 2- Chancroid 3- Glanders 4- Granuloma inguinale 5- Leprosy 6- Lymphogranuloma venereum 7- All invasive fungal infections 8- Melioidosis	9- Mycobacteria 10- Plaque 11- Syphilis 12- Tularemia 13- HSV 14- Dracunculiasis 15- Amoebiasis 16- Leishmaniasis

Eschars	1- Rickettsia spp. 2- Anthrax 3- Tularemia 4- Plague	5- Poxvirus 6- Disseminated aspergillosis 7- Blastomycosis 8- Mucormycosis 9- Leishmaniasis
Oral lesions	1- HSV 2- VZV 3- Enterovirus	4- Syphilis (2ry) 5- Histoplasmosis (ulcer)
Lesions involving the palms and soles	1- Meningococcemia 2- Subacute bacterial endocarditis 3- Syphilis (2ry) 4- RMSF and other rickettsia 5- Rat bite fever	6- Enterovirus 7- VZV 8- Ehrlichiosis

Common types of rash

1- **Erythematous rash**: diffuse or patchy redness of the skin (no skin elevation) witch blanches on pressure e.g.:

- Erythema migrans of Lyme disease
- Measles and german measles
- Scarlet fever
- Drug rashes (ampicillin, sulfa, cephalosporins)

2- **Papular, vesicular and pustular rash:**

- Papules are small elevations of skin e.g. urticaria.
- Vesicles are papules filled with lymph e.g. chicken pox.
- Pustules are vesicles filled with infected material e.g. infected vesicles of chicken pox.

3- **Hemorrhagic rash:** petechial spots or purpura (do not disappear on pressure) e.g. meningococcal meningitis, typhus.

4- **Herpeteform rash:** localized vesicles on erythematous base e.g. herpes simplex or herpes zoster.

5- **Erythema nodosum**

- Streptococcus
- Acute rheumatic fever
- Sarcoidosis
- Tuberculosis
- Leprosy
- Coccidioidomycosis

Important causes of fever with rash (Very Sick Hunter Must Take Entire Complete Adequate Rest)

1- **Very:** viral hemorrhagic fever.

2- **Sick:**

- Spirochetes.
- Scarlet fever & erysipelas.

3- **Hunter:** herpes in immunecompromised patients.

4- **Must:**

- Meningococcal meningitis.
- Measles & German measles.

5- **Take:**

- Typhus
- Typhoid

6- **Entire:** Epstein-Barr virus (infectious mononucleosis).

7- **Complete:** chicken pox

8- **Adequate:** Anthrax.

9- **Rest**

- Rickettsia
- Relapsing fever

Common causes of post-operative fever

Neurosurgery	1- Meningitis 2- Deep vein thrombosis 3- Intracranial hemorrhage 4- Posterior fossa syndrome 5- Hypothalamic dysfunction
Cardiothoracic surgery	1- Pneumonia 2- Endocarditis 3- Mediastinitis 4- Sterna wound infection
Abdominal surgery	1- Abscess 2- Infected hematoma/seroma 3- Anastomotic leak (e.g. bowel, biliary) 4- Peritonitis 5- Pancreatitis 6- Splenoportal thrombosis
Obstetrical or gynecologic	1- UTI 2- Pelvic abscess 3- Postpartum endometritis 4- Pelvic thrombophlebitis 5- Toxic shock syndrome (vaginal packing)
Urologic surgery	1- UTI 2- Deep infection (prostate, perinephric)
Orthopedic surgery	1- Prosthetic infection 2- Infected hematoma 3- Depp vein thrombosis 4- Fat embolism
Vascular surgery	1- Graft infection 2- Postimplantation syndrome 3- Blue toe syndrome (atherothrombotic embolism)

I.P. of selected causes of fever in the returned traveler

Type	< 10 days	10-21 days	>21 days
Bacterial	Bacterial enteritis Bacterial pneumonia Meningococcemia Typhoid & paratyphoid Rickettsiosis (RMSF, African tick bite fever, Mediterranean spotted fever, scrub typhus, Q fever) Relapsing fever Leptospirosis	Typhoid & paratyphoid Rickettsiosis (flea borne, louse borne and scrub typhus, Q fever) Brucella Leptospirosis	Tuberculosis Rickettsiosis (Q fever) Syphilis (2ry) Brucella Bartonellosis (chronic)
Viral	Respiratory viruses (influenza, SARS, chikungunya) Arboviruses (dengue, yellow fever, Japanese encephalitis) Viral hemorrhagic fevers	Acute HIV CMV Flaviviruses Viral hemorrhagic fevers Rabies Measles Histoplasmosis Coccidiodomycosis	Acute HIV CMV EBV Viral hepatitis Rabies
Parasitic	Malaria Amoebic dysentery Fascioliasis African trypanosomiasis (acute)	Malaria Amoebic dysentery Giardia Babesiosis Toxoplasmosis African trypanosomiasis (acute)	Malaria (esp. plasmodium vivax or in the context of ineffective chemoprophylaxis) Babesiosis Amoebic liver disease Schistosomiasis Leishmaniasis Filariasis African trypanosomiasis (chronic)

Incupation period of some infectious diseases

Duration of I.P.	Disease
Short (< 10 days)	Dengue fever Yellow fever Rickettsial infections Plague Falciparum malaria - the incubation period usually quoted for falciparum is 10-14 days. Occasionally it may be as short as 8 days.
Moderate (10 – 21 days)	Malaria African trypanosomiasis Enteric fever (7-21 days) Brucellosis Hepatitis A (2-6 weeks)
Long	Filariasis Leishmaniasis Amoebic liver abscess Hepatitis B (45-160 days)

Causes of new fever in the ICU

Infectious	**Intravascular catheter related**	Cellulitis/abscess Tunnel infection Bloodstream infection Suppurative phlebitis
	Pneumonia	Hospital acquired Ventilator associated
	Miscellaneous	UTI Cl. Difficile infection Surgical site infection Sinusitis Otitis media Parotitis Transfusion related infection Retained foreign body e.g. tampon
Noninfectious	**Drug fever**	Antimicrobias Anticonvulsants Antihistamines Antihypertensives Antiarrhythmics
	Neuroleptic malignant syndrome	Antipsychotics (haloperidol)
	Serotonin syndrome	Selective serotonin reuptake inhibitors
	Malignant hyperthermia	Succinylcholine Halothane
	Withdrawal syndromes	Alcohol Opiates Barbiturates Benzodiazepines
	Miscellaneous	Acalculous cholecystitis Acute myocardial infarction Adrenal insufficiency Cerebrovascular accident Gout Hyperthyroidism (thyroid storm) Intracranial hemorrhage Mesenteric ischemia/infarction Pancreatitis Thromboembolic diseases (DVT/pulmonary embolus) Transfusion reactions Tumor lysis syndrome

Principal conditions for chemoprophylaxis

1- **Benzathine penicillin G injection** → every 2-3 weeks given to patients with history of rheumatic fever to prevent reinfection with streptococcus pyogenes (reactivity)

2- **Single large dose of amoxicillin** → given immediately prior to dental procedures is recommended for patients with congenital or rheumatic heart disease to prevent endocarditis

3- **Oral rifampicin 600 mg** twice daily for 2 days → given to exposed persons during epidemics of meningococcal meningitis

4- **Oral tetracycline** → to prevent cholera

5- **Ampicillin IV** at least 4 hours before delivery → given to women identified as vaginal carriers of streptococcus agalactiae to prevent neonatal sepsis and meningitis

6- **Co-trimoxazole or nitrofurantoin in small doses** → given for about 6 months in case of recurrent urinary tract infections

7- **Chemoprophylaxis in surgery** indicated in the following conditions:

- Large bowel surgery
- Major orthopedic and cardiac surgery
- Amputation of an ischemic limb

8- Bilharziasis

9- Filariasis

Index & Questions

Meningitis

- Management of TB meningitis
- Discuss C/P, diagnosis and management of TB meningitis
- Cryptococcal meningitis
- Meningococcemia
- Parasitic meningitis
- Eosionphilic meningitis: account on management
- Chronic meningitis
- Discuss causes and management of bacterial meningitis
- Give an account on septic meningitis

Brucellosis

- Complications of brucellosis and their management
- Discuss management of complications of brucellosis
- Neuropsychiatric manifestations of brucellosis
- Diagnosis and management of brucellosis of the bone
- Full account on beucella in Egypt
- Discuss management and treatment of brucellosis
- Discuss treatment of brucellosis
- Slide agglutination test
- Discuss clinical picture of brucellosis
- Brucella can be very serious infection, explain clinical picture, diagnosis and treatment of it.

Typhoid fever

- Discuss investigations and treatment of typhoid fever
- Discuss clinical picture, diagnosis and treatment of typhoid fever
- Discuss complications of typhoid fever
- Chloramphenicol resistant salmonella infection
- Interpretation of widal test
- Give full account on typhoid fever

Leprosy سيف الدين

- Erythema nodosum leprosum
- Multiple drug therapy in leprosy
- Discuss treatment of leprosy

Tularaemia

- Management of tularaemia

Bartonellosis and cat scratch disease

Meliodosis

Anthrax

- Discuss types and management of anthrax

Toxic shock syndrome

- Discuss toxic shock syndrome

Acute bacillary dysentery

Antibiotic associated diarrhea/colitis

Food poisoning

Cholera

- Treatment of cholera
- Management of a case of cholera

Tetanus

Plaque

Tuberculosis **(مهم جدا)** **اسامة محمود + سيف الدين**

Infectious mononucleosis

Acquired CMV

Viral heamorrhagic fever

- Account on Lassa fever
- Rift valley fever
- Enumerate the various causes of hemorrhagic fever; describe the management of one of them that can affect the eye

Arboviruses

Encephalitis

HIV **اسامة محمود + سيف الدين (مهم جدا)**

- Discuss pathogens causing diarrhea in HIV
- Infections in immunocomprimized host

Avian flu

- Management of avian flu
- Account on bird flu

Rabies

- Management of a case of rabies
- Pre and post exposure management of rabies
- Describe management of rabies

Coronavirus

- Short note on corona virus

Rickittsial infections

- Discuss C/P, diagnosis and treatment of rickettsiosis
- Discuss the clinical picture & diagnosis of Rickettsia

Spirochaetal infections

- Account on types of relapsing fever

Chlamydial infections

Fungal infections

- Discuss clinical types of candidiasis and their management

Malaria

- Give an account on prophylaxis of malaria
- Chemoprophylaxis of malaria
- Describe the measures taken as a prophylaxis for malaria
- Management of cerebral malaria
- Complications of malignant malaria
- Discuss malignant malaria
- Diagnosis and treatment of falciparum malaria
- Prophylaxis and treatment of malignant malaria
- Management of falciparum malaria in different conditions
- Black water fever: short account
- Treatment of chloroquine resistant malaria

Leishmaniasis

- Discuss kala-azar

Trypanosomiasis

- Management of sleeping sickness
- Romana's sign
- The clinical picture of African trypanosomes is different from the other diseases, mention its presentation and management

Toxoplasmosis

- Management of toxoplasmosis
- Manifestations and treatment of acquired toxoplasmosis
- Describe management of toxoplasmosis

Amoebiasis

- Illustrate the management of a case of cerebral amoebiasis
- Account on cerebral amoebiasis
- Account on amoebic liver abscess

Giardiasis

- Diagnosis and treatment of giardiasis

Nematoda

- Oncocerciasis: eye and skin manifestations and its treatment
- Short note on ocular larva migran

- Discuss various soil transmitted melminthes as regard C/P, diagnosis and treatment
- Give full account on soil transmitted helminthes
- Management of soil transmitted helminthes
- Discuss hyperinfection syndrome
- Treatment of ancylostoma anemia
- Trichinoscopy
- Management of W. bancrofti
- Full account on W. bancrofti
- Illustrate the treatment of W.bancrofti
- Occult filariasis
- Visceral larva migrans
- Diagnosis of strongyloides
- Illustrate the treatment of strongyloidiasis
- Complications of ascariasis
- Management of enterobiasis
- Diagnosis and treatment of tissue nematodes
- Diagnostic nematode stages passed in human stool
- Describe different clinical presentations and complications that may result from ascaris infection and mention the methods of diagnosis and treatment

Trematoda

- S.mansoni, S. hematobium infection: compare morbidity
- Discuss fascioliasis
- Discuss C/P, investigations and treatment of Fasciola hepatica
- Describe the management of a case of Fasciola hepatica of the liver
- Katayama syndrome
- Treatment of schistosomiasis
- Discuss ectopic schistosomiasis
- Discuss invasive & non-invasive methods for the diagnosis of portal hypertension

Cestoda

- Discuss hydatid disease in man
- Cestode stages passed in human stool
- Enumerate larvae of cestodes which can present in human tissues: discuss prevention and treatment of 2 diseases caused by them

Entomology

- Medical importance of xenopsylla cheopis
- Diagnosis and management of scabies

Sexually transmitted diseases

- Chancer
- Painful genital ulcers

Tropical ulcer

- Account on leg ulcers

Dermatological manifestations in the tropic

Bruli ulcer

Acute flaccid and spstic paralysis

Fever of unknown origin **سيف الدين أو عبدالله ابو جبل**

- Diagnostic studies in a case of FUO

Environmental health hazards

- Discuss various heat illnesses
- What various heat related disorders? Discuss diagnosis and treatment
- Discuss heat hyperpyrexia
- Discuss briefly regulation of body temperature: explain the mechanism of fever
- Discuss environmental hazards of a desert safari

Chemotherapeutics and vaccination **اسامة محمود أو سيف الدين**

- Role of chloramphenicol in fever
- Define and describe antibiotic failure and its management and its laboratory evaluation
- Ivermectin
- Quinolones
- Antibiotics avoided in pregnancy and why?
- Azole group of antifungal drugs
- Enumerate various oral vaccines; explain their side effects and doses in addition to precaution for an especial group of patient.

Vitamin and minerals deficiency **اسامة محمود أو سيف الدين**

- Account on beri-beri
- Iron deficiency anemia
- Hypochromic microcytic anemia
- Neuropsychiatric manifestations of pellagra

Collections

- Enumerate ocular manifestations in the tropics and discuss one of the most serious conditions
- Discuss intracorpuscular infections
- Account on diarrhea caused by protozoal infection other than amoebic infection
- Management of a case of unilateral edema
- Parasitic infections causing endemic hemoptysis
- Parasitic diseases of the lung: enumerate causes, and discuss diagnosis and treatment
- Enumerate helminthic parasites causing jaundice, mention infective stages, mode of infection of each. Duscuss C/P, diagnosis and treatment of one of them
- Mention protozoa encountered in liver biopsy specimens. Discuss infective stage, mode of infection of each. Give the diagnosis and treatment of one of them
- Discuss the diagnosis of protozoal liver diseases **لورانس**
- Discuss clinical picture, diagnosis, treatment of spirocheatal disease of the liver **لورانس**

- Enumerate helminthic parasites causing hepatomegaly. Mention mode of infection of each. Discuss pathogenesis and clinical picture of one of them
- Fever with descending paralysis
- Fever with convulsions in 25 years old femal: proper management
- Discuss fever presenting with coma
- Fever 10 days with just palpable splenomegaly
- Enumerate causes of fever with jaundice
- Fever with haemorrhagic rash: diagnosis and treatment
- Mention different types of skin rashes and the infectioud diseases that cause them
- Enumerate causes of fever accompanied by different types of skin rashe. Describe clinical picture, diagnosis and management of one of them
- Discuss recurrent fevers
- Discuss emerging fevers
- Infections from mother to fetus: enumerate causes and discuss management
- Traveler's diarrhea
- How to reach diagnosis in a case presented with tenesmus
- How to manage a case presented by fever & lymphadenopathy in an adult patient

References:

1- Lecture notes of tropical medicine 6th editin
2- The Washington manual of infectious diseases: 2nd edition
3- A guide book of tropical medicine and infectious diseases: by Salah Saif El Din and Fathy Abdel Wahab
4- Lecture notes of internal medicine: infectious and tropical diseases by Osama Mahmoud